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TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) WITH PREDNISONE

William Dameshek, M.D., Fernando Rubio Jr., M.D.
John P. Mahoney, M.D., W. Harrison Reeves, M.D.
and
Leonard A. Burgin, M.D., Boston

Prednisone was used in the treatment of 30 consecutive patients with ITP (idiopathic thrombocytopenic purpura) under conditions that permitted the establishment of a satisfactory base line for metabolic and hematological studies, especially as to platelet count and other coagulation studies. Eleven cases were of the "acute," and 19 cases of the chronic type. The initial dose of prednisone varied between 20 and 150 mg. per day, given by mouth. The results ranged from complete absence of response to sustained remission without apparent need of further treatment. In 22 of the 30 cases the platelet count rose from the initial low values to normal in 6 to 150 days. Much individual adjustment of dosage was necessary. Maintenance dosages ranged from 2.5 to 15 mg. per day, but in eight patients it was possible to withdraw the prednisone entirely after establishing a normal platelet count. Splenectomy was performed in five patients of this series but was followed by complete, sustained remission in only one case. These results lead to the conclusion that in the treatment of ITP chief reliance should be placed upon such measures as prednisone therapy and transfusions, splenectomy being reserved for the occasional severe cases that do not respond to medical measures.

THE TREATMENT of idiopathic thrombocytopenic purpura (ITP) has never been fully satisfactory. Kaznelson's [1] major contribution of 1916 indicated that splenectomy could induce a spectacular increase in blood platelets. However, as experience with this operation increased, it became apparent that the rise in platelets was often a transient one and that relapses to the original low levels might take place three months, one year, or even several years after splenectomy.[2] There was, furthermore, the not inconsiderable risk attending the operative procedure, particularly if this was undertaken in an acute bleeding phase of the disease and as an emergency measure.[3] In recent years, the danger of fatal, usually cerebral, bleeding in the course of ITP has been considerably reduced by the introduction of two "medical" methods, i. e., the use of siliconized bottles or plastic bags for transfusion of fresh whole blood, including viable platelets, and the use of ACTH and the corticosteroid hormones. It has been adequately demonstrated that with these two measures even the acute cases of ITP, with severe bleeding into the skin and mucous membranes, can be kept under good control and tided over the hemorrhagic crisis, usually a matter of a few to several days.[4]

The effects of ACTH and later of cortisone on the bleeding disorder appeared to be mediated largely through the small blood vessels.[5] Thus, striking improvement in the bleeding tendency usually took place even without a rise in platelets. In some cases, however, a marked rise in platelets oc-

From the Blood Research Laboratory, unit of the Ziskind Laboratories, New England Center Hospital, and the Department of Medicine, Tufts University School of Medicine. This work was done during the tenure of a U. S. Public Health Service, National Cancer Institute Traineeship by Dr. Mahoney, and a U. S. Public Health Service, National Heart Institute Postdoctoral Fellowship by Drs. Reeves and Burgin.

curred shortly after institution of steroid therapy. Whether this was due to the therapeutic agent or represented a coincidental spontaneous rise in blood platelets was often uncertain, especially in the acute cases, although in some cases, there seemed little doubt that the rise in platelets was due to steroid administration. Our own studies indicated that, although ACTH and cortisone were of distinct value in diminishing bleeding, they were of uncertain value in initiating a rise in platelets.[4] Thus, the use of these agents in ITP during a period of approximately five years led us to conclude that splenectomy was still the specific method of therapy in those cases continuing at low platelet levels for more than four to six months and that steroid therapy was chiefly valuable as a nonspecific "antihemorrhagic" agent.[4]

In the past few years, as it became increasingly apparent that the initial remissions after splenectomy were followed by increasing numbers of relapses, a reevaluation of the effects of the steroids in ITP, with particular reference to the blood platelet count, seemed desirable, especially when the new steroid, prednisone (Meticorten), became available. Since it was possible to use this material in large, even massive doses and with minimal water retention, a series of consecutive cases of ITP was treated. It was soon evident that striking rises in platelet level took place with great consistency, whether the patient's condition was acute or chronic or had relapsed after splenectomy. In this paper, we report the results of the use of prednisone in the treatment of 30 consecutive cases of ITP treated during 1955 to 1957. Analysis of the results indicates that the treatment of ITP by splenectomy may eventually become of secondary importance as "medical" therapy for this disorder is increasingly perfected.

Therapy with Prednisone

Therapy with prednisone was instituted after an appropriate baseline of hematological values had been obtained, usually with the patient in the hospital. Prednisone was supplied in slotted 50-mg. tablets which were given by mouth, usually in divided doses. In addition to hematological and hemorrhagic studies, various clinical observations were made, and in a number of cases detailed metabolic, renal, and electrolyte studies were performed. Platelet counts were performed by the method described by one of us,[5] in which the normal platelet level varies from 400,000 to 800,000 per cubic millimeter. The initial dose of prednisone varied from case to case; doses of 20 to 250 mg. per day were used. After a normal platelet count had been established, the dose of the drug was decreased and then gradually reduced to levels of 2.5 to 15.0 mg. or withdrawn entirely. In a few cases, the dose was titrated to fit the rising or falling platelet level. Cases were classified as "acute" or "chronic" according to the criteria set forth in a previous paper,[1] with the reservation kept in mind that the distinction between an "acute, self-limited" case and a "chronic" one is often difficult and at times impossible to determine.

The results of therapy in this group of patients with idiopathic thrombocytopenic purpura are summarized in the table and figure 1. The terms complete remission, incomplete remission, and slight or no response refer to the platelet count. All the patients who had complete remissions obtained and maintained normal platelet counts. Those who developed incomplete remissions had platelet counts from one-third to nearly normal values. In every patient, there was prompt and marked improvement in the hemorrhagic symptoms and return of the bleeding time to normal or nearly normal values. This effect always preceded or occurred independently of changes in the platelet level. The initial platelet counts in this series of cases were at extremely low levels: 0 to 53,000 per cubic millimeter with three exceptions, patients 20, 21, and 25 whose platelet counts were 90,000, 100,000, and 82,000 respectively. Eleven cases were of the acute type and nineteen were chronic. Of the latter, two patients had had relapses after previous splenectomy.

Normal platelet counts were attained in 6 to 150 days in 22 of the 30 cases. These took place in 10 of the 11 acute cases after an average of 22.4 days of treatment. In the chronic cases, completely normal platelet counts were obtained after an average of 50 days of therapy in 12 of the 19 cases. In addition, in two other cases classified as chronic (1 and 29) the platelet level rose to almost normal values of 374,000 and 366,000 per cubic millimeter respectively. In the remaining six patients, the platelet level was considerably improved in two, and little or no change occurred in the platelet count in four, two of whom (cases 17 and 20) received massive doses of steroid therapy (200 to 250 mg. daily). Initial response to therapy with prednisone took place very quickly in 10 of the 11 patients with acute conditions, as indicated by a definite increase in platelets (usually to one-fourth or one-third of normal values), and averaged 9.4 days. In the 12 patients with chronic conditions who attained normal platelet counts, the results were more variable—from 6 to 60 days with an average of 15.3 days. In the two patients who had had previous splenectomy, complete remissions occurred at 14 and 30 days respectively.

When the doses of prednisone were reduced (2.5 to 10 mg. daily), reduction in the platelet count took place frequently. Of the 24 patients who obtained normal or nearly normal platelet counts and in whom the drug was subsequently reduced or withdrawn after the initial course of therapy, relapse to previous low platelet levels took place in 7 patients in 18 to 120 days. The actual intervals were as follows: 20, 18, 60, 22, 24, 120, and 18 days.

V 1
195

It is of interest that in five of these cases the relapse occurred in approximately 20 days. The longest interval occurred in the patient in case 5, who had previously undergone splenectomy. In an additional five cases, a modest but significant drop in platelet level took place when the dose of prednisone was reduced to low levels, although the platelet count never approximated the pretreatment low values. In these cases, too, the drop in platelet level took place 10 to 30 days after the prednisone dosage had been reduced.

When relapse had occurred, after either withdrawal of prednisone or reduction to low dosage, therapy with higher dosage was again instituted and excellent responses again took place (seven out of the seven above-mentioned cases). In those cases in which sufficient data could be obtained, the new remission took place within 10 to 20 days after institution of therapy. It was then possible in most cases to adjust or maintain the platelet count at either normal or at somewhat less than normal values by variation of the maintenance dose of steroid between 2.5 to 15.0 mg. daily. Because of the well-known effects of continued steroid therapy, the attempt was always made to reduce the dosage to at least 5 to 10 mg. daily. In several instances, when normal levels of platelet counts had been reached and had been maintained by a dose of

Summary of Clinical Data in Thirty Patients with ITP Treated with Prednisone

Case No.	Age, Yr.	Sex	Initial Platelet Count/ Cu. Mm.	Dose, Mg.		Initial Response to Therapy		Subsequent Course, Present Status
				Initial	Largest	Days	Platelet Level/ Cu. Mm.	
1	8	M	9,000 Chronic*	30	Same	8	374,000	Relapse without therapy; incomplete remission; maintenance therapy required
2	17	M	12,500 Acute*	50	100	16	450,000	Complete remission sustained without further therapy
3	13	F	21,300 Acute	60	Same	6	630,000	Relapse without therapy; splenectomy; complete remission without further therapy (see case report)
4	13	M	25,000 Acute	40	150	30	400,000	Complete sustained remission without further therapy
5	27	F	35,000 Chronic†	30	Same	60	468,000	Sustained remission with maintenance therapy (see case report)
6	73	M	8,000 Chronic	80	Same	9	450,000	Relapse without therapy; incomplete remission; no further therapy given due to psychiatric disturbance.
7	7	F	7,000 Chronic	20	Same	6	480,000	Sustained remission; no further therapy required
8	33	F	23,000 Chronic	100	Same	7	574,000	Sustained remission; no further therapy required
9	49	F	8,000 Acute	100	Same	4	450,000	Relapse on reduced dosage; splenectomy; incomplete remission; refused further therapy (see case report)
10	50	F	19,000 Acute	150	Same	6	580,000	Relapse without therapy; second remission sustained with maintenance therapy (see case report)
11	62	F	12,000 Chronic	20	100	75	400,000	Sustained remission with maintenance therapy (mild diabetes and hypertension)
12	23	F	22,000 Chronic	50	Same	15	456,000	Sustained remission; no further therapy required
13	40	F	9,000 Acute	100	Same	6	550,000	Relapse without therapy; splenectomy; relapse third remission sustained with maintenance therapy (see case report)
14	43	F	15,000 Chronic†	100	Same	60	550,000	Sustained remission with maintenance therapy (see case report)
15	3	F	5,000 Acute	20 with ACTH	Same	8	570,000	Sustained remission; no further therapy required
16	14	M	19,000 Chronic	50	Same	10	1,000,000	Relapse without therapy; second remission with therapy sustained; no further therapy required
17	45	F	9,000 Acute	30	250	75	30,000	Very slight response; splenectomy; incomplete remission; no further therapy required
18	43	F	13,000 Chronic	50	Same	30	430,000	Sustained remission with maintenance therapy
19	26	F	8,000 Chronic	100	Same	60	450,000	Sustained remission with maintenance therapy
20	40	M	90,000 Chronic	50	200	90	120,000	Prompt but short lived remission with splenectomy; no further therapy required (see case report)
21	43	F	100,000 Chronic	20	Same	150	460,000	Complete remission with maintenance therapy
22	19	F	4,000 Acute	75	Same	120	510,000	Complete remission with maintenance therapy
23	5	M	58,000 Chronic	25	50	120	150,000	Incomplete remission with maintenance therapy for four months
24	47	M	42,000 Chronic	50	Same	21	200,000	Incomplete remission with maintenance therapy for four months
25	53	F	82,000 Chronic	50	Same	11	650,000	Complete remission with maintenance therapy (hypotension)
26	1½	F	30,000 Acute	25	Same	21	620,000	Complete remission with maintenance therapy
27	38	M	"None" Acute	100	Same	7	554,000	Complete remission with maintenance therapy
28	11	F	30,000 Chronic	15	50	8 mo.	50,000	No response
29	28	F	30,000 Chronic	50	100	120	300,000	Incomplete remission with maintenance therapy
30	1	M	30,000 Chronic	20	50	6 mo.	40,000	Very slight response with maintenance therapy

* "Acute" and "chronic" refer to diagnosis at time of our first examination.
† Postsplenectomy.

5 mg. of prednisone daily, it was a difficult matter to decide whether further therapy should be continued. No exact rule was followed, and in some cases withdrawal of steroid was eventually regretted since later it was again necessary to return to the relatively high starting dose of steroid.

NATURE OF RESPONSE	NUMBER OF PATIENTS	SUBSEQUENT COURSE	NUMBER OF PATIENTS
COMPLETE REMISSION	20	SUSTAINED REMISSION (2-24 months) NO FURTHER THERAPY	6
PREVIOUS ⑤ 2 SUBSEQUENT ⑤ 2		SUSTAINED REMISSION (6-24 months) WITH MAINTENANCE THERAPY	10
		REMISSION FOLLOWED BY RELAPSE ⑤→ REMISSION	1
		RELAPSE, 2nd REMISSION WITH ⑤ RELAPSE, 3rd REMISSION	1
INCOMPLETE REMISSION * PREVIOUS ⑤ 0 SUBSEQUENT ⑤ 1	6	NO FURTHER THERAPY	1
		MAINTENANCE THERAPY	4
		INCOMPLETE REMISSION WITH ⑤	1
SLIGHT RESPONSE PREVIOUS ⑤ 0 SUBSEQUENT ⑤ 2	4	INCOMPLETE REMISSION WITH ⑤	2
		CONTINUED THERAPY	2

Fig. 1.—Summary of results in 30 patients with ITP treated with prednisone. S = splenectomy.

In eight cases, it was eventually possible to discontinue prednisone therapy completely without a further drop in platelet level. Of these eight cases, four were of the chronic variety, in which normal platelet counts are rarely noted without therapy. We anticipate that eventually we will be able to discontinue prednisone therapy in many of the patients who are in a state of complete remission on maintenance therapy. The following case report illustrates some of these points.

Case 10.—A 50-year-old woman was admitted to the New England Center Hospital on Aug. 26, 1955. She had noted fleeting purpura and easy bruisability three months prior to admission. Three weeks before admission, there was a marked accentuation in her course with increasing purpura. Physical examination revealed scattered ecchymoses and a few petechiae of the buccal mucosa. Laboratory studies showed a platelet count of 19,000 per cubic millimeter with an increased number of apparently inactive megakaryocytes in the bone marrow. The remainder of the blood picture was within normal limits. Therapy with prednisone, 150 mg. per day, was started, and there was a very rapid response in the platelet level; within two days, the platelet count was 100,000 and within six days, 580,000 per cubic millimeter. The medication was gradually tapered off and discontinued after nine weeks. Twenty-four days after prednisone was withdrawn the platelet count dropped abruptly. A second course of the therapy again produced a quick rise in platelet values to normal. A complete remission has been maintained for 20 months (October, 1957) with the continued use of prednisone in a dose of 5 mg. daily (fig. 2).

Splenectomy as Therapeutic Measure in Five Cases

Case 17.—A 45-year-old housewife was first admitted to the New England Center Hospital on Aug. 23, 1956, having had a purpuric rash for one month, which had not responded to prednisone in a dose of 15-20 mg. daily. She had taken no other medicament except for digitalis, 0.1 Gm. daily, for chronic auricular fibrillation in association with rheumatic mitral stenosis. She had never had quinidine. On examination, the patient appeared healthy and had excellent color. Many petechiae of the gums and mucous membranes were present. Auricular fibrillation (rate ± 90) was present. There was a short mitral diastolic murmur. No evidence of cardiac decompensation was present. The skin was covered with numerous ecchymoses and petechiae. The blood platelet level was extremely low (9,000 per cubic millimeter) in the presence of otherwise normal blood cell counts. The bone marrow contained normal numbers of apparently inactive megakaryocytes.

Prednisone was given in a dose of 100 mg. daily for 14 days without effect on the platelet level. There was a diminution in bleeding tendency, although the bleeding time continued to be somewhat prolonged. Prednisone therapy was then continued with a dose of 50 mg. daily for one month, again without effect. The patient was then rehospitalized and the dose of prednisone raised to 250 mg. daily for 12 days. Again no significant rise in platelets took place, although the bleeding time became normal. Because of the lack of response, splenectomy was finally carried out approximately three and one-half months after the onset of her illness, cortisone being given intramuscularly just before operation and during the immediate postoperative course.

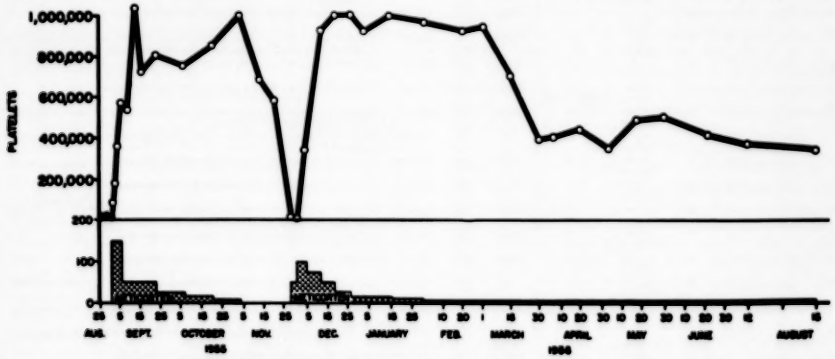

Fig. 2.—Blood platelet levels during prednisone therapy for ITP (case 10).

Cortisone was then gradually withdrawn, and the platelet level rose slowly during the first postoperative month to normal values. The end-result in this case remains uncertain, since there has been a steady drop in her platelet level (fig. 3).

CASE 3.—A 13-year-old girl suddenly developed a spontaneous episode of epistaxis lasting for one-half hour three months prior to admission. There were petechiae, numerous ecchymoses, and mild menorrhagia. Physical examination on admission was normal save for numerous ecchymoses scattered over the abdomen, chest, and extremities. The platelet count was extremely low (20,000 per cubic millimeter), and the bone marrow preparation showed increased numbers of apparently inactive megakaryocytes. The patient was given two transfusions of fresh blood collected in plastic bags and ACTH in a dose of 100 units daily for four days, after which prednisone, 60 mg. daily, was given. The platelet count rose rapidly in 12 days to 750,000 and in about a month to 1 million per cubic millimeter. All hemorrhagic manifestations ceased. When the dose of prednisone was gradually reduced and then withdrawn, the platelet count again fell to the previously very low levels.

During the period of prednisone therapy, the patient gained 20 lb. (9 kg.) in weight and showed the features of marked hyperadrenocorticism. When the hemorrhagic manifestations recurred, prednisone was again resumed in doses of 10-15 mg. daily. There was a transitory rise of platelets to 400,000, but the Cushingoid reaction was again quite marked. Splenectomy was then performed, and cortisone was given intramuscularly in a dose of 100 mg. daily. The platelet count rose rapidly to levels of 1,500,000 to 3,500,000 per cubic millimeter and then leveled off at 1,400,000 to 1,700,000 without further treatment (fig. 4).

Although an excellent platelet response took place in this apparently acute case with steroid therapy, the development of symptoms of marked hyperadrenocorticism interfered with continued therapy with prednisone, and splenectomy was therefore performed. An extreme thrombocytosis developed, perhaps due partly to the corticosteroids, perhaps to the splenectomy, or to a combination of those two procedures. This case was treated early in our series, and in retrospect, the actual necessity for splenectomy in a child of 13 only seven months after the development of the first attack of bleeding is open to question, since at the time of splenectomy, no obvious hemorrhagic manifestations were present, and complete remission in such cases may occur even at the end of a year.

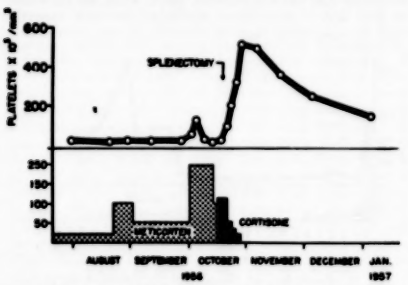

Fig. 3.—Failure of blood platelet levels to respond to prednisone therapy for ITP (case 17).

CASE 9.—A 49-year-old woman developed petechiae and ecchymoses about one month prior to her admission. Save for these, physical examination was negative. Blood studies showed 8,000 platelets per cubic millimeter, and bone marrow aspiration revealed normal numbers of megakaryocytes, which seemed inactive. On prednisone therapy (100 mg. daily), the platelet count rose to 450,000 per cubic millimeter, but when the dose of steroid was reduced to 50 mg. daily, the platelet count again dropped to its original low level. Splenectomy was decided upon because of the apparent failure of prednisone therapy. The platelet count rose to 800,000 per cubic millimeter and remained at this level for two months. However, six months after splenectomy, the platelet count had dropped to 200,000 and nine months after operation there was a further drop to approximately 100,000 per cubic millimeter.

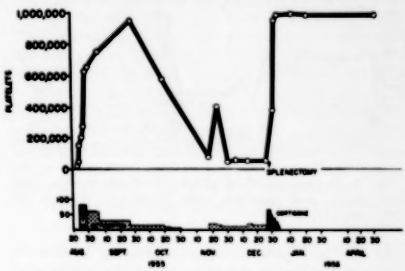

Fig. 4.—Excellent and sustained remission of blood platelet levels after splenectomy, which may have been unnecessary (case 3).

A good response in this case took place when prednisone in a dose of 100 mg. daily was given, but relapse occurred on 50 mg. Splenectomy was apparently productive of a good remission, but six months after splenectomy the patient was again in relapse. Thus, splenectomy was by no means the answer to the problem of thrombocytopenia in this case. This case may also be considered a relative failure of prednisone therapy, since on a dosage of 50 mg. daily relapse in platelet level took place.

CASE 13.—A 40-year-old woman suddenly developed purpura, bleeding gums, and menorrhagia about four weeks before admission. Examination was negative except for numerous ecchymoses. The platelet count was practically nil, although the bone marrow showed numerous apparently inactive megakaryocytes. Treatment with prednisone, at first in a dose of 100 mg. daily, was quickly followed by a rise in platelet count to 600,000 per cubic millimeter. On 5 mg. of steroid daily, the platelet count was maintained at levels between 400,000 to 600,000, but when prednisone therapy was discontinued, the platelet count dropped to 50,000 per cubic millimeter. With reinstitution of prednisone therapy in smaller doses, the platelet level did not improve significantly, but when the dose was raised to 75 mg. daily there was again a rise in platelet count to 1 million per cubic millimeter. It was felt that, since large doses were neces-

sary to induce a normal platelet level, splenectomy should be performed. This was carried out in March, 1956, but was followed by a gradual relapse in the bleeding tendency and thrombocytopenia. In September, 1956, prednisone, 30 mg. daily, was again instituted and resulted in a striking remission within eight days. The dose of prednisone was then gradually reduced to 7.5 mg.; by trial and error it was eventually found that a reasonably normal platelet level could be maintained on 10 mg. of the steroid (fig. 5).

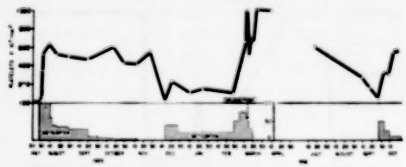

Fig. 5.—Relapse in blood platelet levels six months after splenectomy, and remission with prednisone therapy for ITP (case 13).

In this case prednisone was effective in two relapses, but splenectomy was nevertheless performed and prednisone withdrawn. Relapse occurred after splenectomy after a six-month remission. Splenectomy in this case was without lasting benefit, but when prednisone therapy was again resumed, the platelet count rose to normal and has remained reasonably normal since on small daily doses of prednisone (5-10 mg.).

Case 20.—A 40-year-old man was referred in November, 1956, for therapy of idiopathic thrombocytopenic purpura of at least 18 years' duration. The patient had first noted spontaneous petechiae and ecchymoses in 1938 and since then had never been free of them. There had been no other hemorrhagic symptoms except for profuse bleeding after minor surgical procedures including dental extractions. In October, 1956, a biopsy of a benign mandibular cyst was performed at another hospital, and the patient experienced profuse bleeding. The platelet count at that time was stated to be between 20,000 and 40,000 per cubic millimeter. Prednisone in a dose of 15-20 mg. per day was given with a marked improvement in the bleeding tendency. Further mandibular surgery was contemplated in the future.

On examination by us, the patient showed numerous petechiae about both ankles and marked pigmentation of the shins and dorsa of both feet; in addition, several small ecchymoses were present. The remainder of the examination was negative. The blood cell counts were as follows: hemoglobin level, 14.5 Gm. per 100 cc.; red blood cell count, 5,200,000; white blood cell count, 7,200, with a normal differential count. The platelets numbered 90,000 per cubic millimeter. The bone marrow contained numerous megakaryocytes although there appeared to be but little platelet production. The Coombs test was negative and no platelet agglutinins were demonstrated.

On Nov. 6, 1956, the dose of prednisone was increased to 50 mg. per day. Three weeks later the platelet level was 100,000 per cubic millimeter. Prednisone was increased to 200 mg. per day for 10 days without significant change in the platelet level. The dose was gradually reduced to 50 mg. per day, but by the middle of February, 1957, no significant rise had occurred in the platelet level. On Feb. 19, 1957, splenectomy was performed with the aid of two transfusions of fresh blood from plastic bags. On the next day the platelets numbered 1,200,000 per cubic millimeter. Prednisone, in a dose of 25 mg. per day, was continued for two weeks and then gradually reduced and eventually withdrawn in March. Excision of the mandibular cyst was carried out in April without incident. By July, the patient's platelet count had dropped to 300,000 per cubic millimeter, but he was entirely free of bleeding manifestations.

In this example of chronic ITP there was a three-month course of prednisone therapy in large doses with little effect on the platelet level. Splenectomy brought about a prompt and striking rise in platelet count. Five months later, the platelet level was somewhat below normal, indicating that the ultimate result of splenectomy was uncertain.

Therapy with Prednisone After Previous Splenectomy

Case 5.—A 27-year-old woman developed severe menorrhagia and spontaneous ecchymoses four months before admission to her local hospital. The uterine bleeding was massive, requiring 13 transfusions, and subtotal hysterectomy was performed. After operation, thrombocytopenia was discovered for the first time and the patient was treated with cortisone in a dose of 400 mg. daily. An improvement in bleeding tendency took place, but there was no rise in platelet count. Because of this, the patient was referred to our care. Examination revealed numerous ecchymoses and petechiae of skin and mucous membranes, and there was continued vaginal bleeding. Neither the liver nor spleen was palpable, and the remainder of the examination was negative. The platelet count was 13,000 per cubic millimeter; the marrow aspiration revealed normal or inactive megakaryocytes, without apparent platelet production. Splenectomy was performed in June, 1954, with a transient rise in platelets to 500,000 per cubic millimeter, but within 15 days the platelets had again dropped to low levels (60,000-80,000). Cortisone, at first in a dose of 200 mg. daily, later in smaller doses, was given but without effect. The drug was eventually withdrawn on Dec. 10, 1954.

The patient was relatively free of hemorrhagic symptoms from that date until September, 1955, when she again developed severe ecchymoses and petechiae with bleeding from the nose, gums, and vagina. The platelet count at this

Fig. 6.—Remission of blood platelet levels with prednisone therapy for ITP after failure to respond to splenectomy and cortisone therapy (case 5).

time was approximately 40,000 per cubic millimeter. Prednisone was given in an initial dose of 30 mg. daily, subsequently 20 and 15 mg. daily. There was a quick improvement of bleeding symptoms, and the platelet count rose in two months to 468,000. When the prednisone dosage was reduced to 10 mg. daily, the platelet count dropped to 300,000. The dose of prednisone was raised to 25 mg. daily,

V 1
195

and one month later (March, 1956) the platelet count rose to 1 million. Prednisone was gradually tapered to 5 mg. daily, and on this dosage there was a slow but progressive drop in platelet count to 350,000 (November, 1956) but without recurrence of bleeding manifestations (fig. 6). During the past year (November, 1957), the platelet count has remained between 350,000 and 450,000 per cubic millimeter. Prednisone has been continued in a dose of 5 mg. daily.

In this case, as with many others presenting severe menorrhagia due to thrombocytopenia, hysterectomy had been performed without benefit. Splenectomy was thereupon performed with only a minor remission lasting for about two weeks. When relapse occurred, prednisone was given with an excellent response. Withdrawal of prednisone was followed by relapse, and again remission was secured when prednisone was resumed. Eventually, small doses of prednisone sufficient to keep the platelet count at nearly normal values were used, and the patient remained free of all hemorrhagic manifestations. This case illustrates several points: (1) the ineffectiveness of cortisone in raising the platelet count, (2) the ineffectiveness of splenectomy, (3) the effectiveness of prednisone, and (4) the lack of necessity for maintaining the platelet level at completely normal values, thus allowing the use of very small doses of prednisone for maintenance.

Case 14.—A woman, aged 43, developed the typical features of ITP in 1943, and splenectomy was performed (in Montreal). There was apparently complete remission until 1948 when all the various manifestations of the disease recurred in great severity. Between 1950 and 1956, ACTH and cortisone in moderate doses were used either intermittently or regularly without significant effect on the platelet count, which varied between 20,000-50,000 per cubic millimeter. There was constant severe menorrhagia and many ecchymoses of the skin. In September, 1954, when first seen in Boston, the patient had all the features of ITP both in blood (platelet count, 26,000 per cubic millimeter) and bone marrow; nothing specific was recommended. In June, 1956, when she returned for reevaluation, she complained of severe menorrhagia, some bleeding from the nose and gums, and frequent ecchymoses and petechiae. The platelet count was 30,000 per cubic millimeter. Bone marrow aspiration revealed marked megakaryocytosis with apparently reduced activity in platelet production. Therapy with prednisone, at first in a dose of 100 mg. daily, then gradually reduced to 25 mg. daily, resulted in a rise in the platelet count to 275,000 in two weeks and to 550,000 in the course of two months. With continued therapy of 10 mg. of steroid daily, the platelet level rose to 800,000 per cubic millimeter, and the dose was reduced to 5 mg. daily. There was a complete disappearance of all bleeding tendency and the development of a scanty menstrual flow (fig. 7).

In this patient who had a relapse after splenectomy for ITP with severe bleeding tendency, the continued use of ACTH and cortisone, in the dosages used, was without effect, but prednisone was productive of an excellent remission.

Except possibly in three cases, a comparative study of the effects of prednisone and cortisone on the platelet level could not be made. In case 5, treatment with cortisone in a dose of 400 mg. daily was instituted when thrombocytopenia was first found after hysterectomy. There was an improvement in the vaginal bleeding, but no effect on the platelet count was noted. Later, after the failure of splenectomy to raise the platelet level, cortisone was again given in a dose of 200 mg. daily, again without significant effect on the platelets. However, when prednisone was given in a dose of 25-30 mg. daily, a dramatic rise in platelets took place. In this case, the superiority of prednisone over cortisone seemed unequivocal. In case 7, ACTH, followed later by cortisone, was productive of a striking remission, but when cortisone therapy was discontinued, the platelets fell to their original low values. Prednisone in relatively small doses was followed by another remission, which has been sustained for six months, although therapy was discontinued. Since ACTH was used first and was followed by a rise in platelets before cortisone was given, a comparison of prednisone-cortisone effects is impossible here.

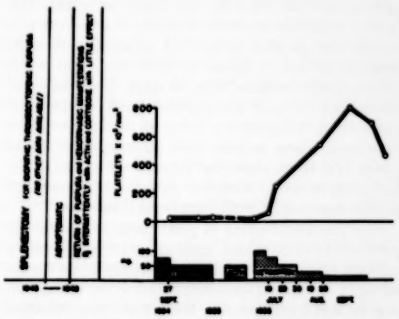

Fig. 7.—Excellent remission of blood platelet levels with prednisone therapy for ITP 13 years after splenectomy.

In case 14, with relapse after splenectomy, moderately large doses of ACTH and cortisone were used intermittently for a few years but without any significant effect on the platelets; however, when prednisone was used, a striking remission took place.

From these three cases, a definite comparison of cortisone-prednisone effects is possible only in case 5, in which large doses (400 mg.) of cortisone were without effect before splenectomy, and 200 mg. of the same steroid were ineffective after splenectomy; prednisone in relatively small doses (25-30 mg.) resulted in a marked rise in platelets. Prednisone was also strikingly effective in case 14, after the previous ineffectiveness of cortisone therapy; here, however, a dosage effect may have been operative since prednisone was used initially in a dose of 100 mg. daily.

Comment

There can be little question regarding the rather consistent effect of prednisone in causing striking rises in the platelet count in this series of cases of ITP. Of the 30 cases, completely normal platelet levels were attained in 22 (73%). The effect of prednisone on the platelets was noted not only in 10 patients out of the 11 acute cases (90%) in which spontaneous remissions are a common occurrence, but also in 12 patients out of the 19 chronic cases (60%), as well as in those who had had a relapse after splenectomy. The time interval between the beginning of prednisone therapy and the development of a well-defined rise in platelets was relatively constant, averaging 9 days in the acute cases and 16 days in the chronic ones, whether or not splenectomy had previously been done. There was furthermore a rather striking constancy in the time interval between withdrawal of therapy and the reappearance of the thrombocytopenia. This was approximately 20 days in the cases in which this matter could be studied. Similarly, in the cases in which the platelet count fell when the dose of prednisone was reduced to 5-10 mg., low levels were attained within 10 to 30 days. This ability of prednisone to raise the platelet level has in some cases been of life-saving value, as in the case of an extremely obese woman with severe hypertension (case 11). Here, expectant therapy with prednisone led to an eventual complete remission; splenectomy in this case might well have been disastrous.

The consistent effect of prednisone in raising the platelet level in these cases of ITP has been a striking phenomenon; its mechanism is by no means obvious. A direct (inhibitory?) effect on the spleen can be ruled out because the steroid was effective even in the absence of the spleen. Was the effect due to a stimulatory one on the megakaryocytic production of platelets or to a reduction in thrombocytopenic factor, which is presumably of immunological nature? This is by no means clear and requires further study, but in view of the demonstration by several groups of workers of an immunological mechanism in ITP[8] and the well-known effects of the corticosteroids in inducing a reduction in antibody concentration, not only with the infectious antibodies but with the antibodies of "autoimmune" hemolytic anemia, it seems more likely to us that prednisone acts through depression of antibody production. We have commented previously on the many similarities between autoimmune hemolytic anemia and ITP.[9]

The striking rise in platelets in acute ITP in approximately 9 days after the beginning of prednisone therapy, and in chronic ITP in approximately 22 days, and the fall in platelets in approximately 20 days when the steroid therapy was discontinued may also be cited as indicating that the effects of prednisone were on antibody formation (and therefore on its concentration in the blood stream) with the ultimate effect as noted on the platelets. Thus, the latent period occurring before the rise in platelets could be due to the time required to reduce antibody sufficiently so that platelet survival time could become relatively normal. Likewise, the latent period occurring between withdrawal of prednisone and the drop in platelets might conceivably be due to the ensuing gradual rise in antibody concentration in the blood and its ultimate effect on the platelets.

The relative constancy of the effect of prednisone as compared to the inconstant effects of ACTH and cortisone is of considerable interest. Although it is impossible to make any completely definitive statement as to the relative merits of prednisone versus ACTH or cortisone in this series of cases, we have been considerably impressed with the relatively certain and predictable effects of prednisone, whereas in our previous use of ACTH and cortisone, even in large doses, the results on the platelet level were decidedly uncertain. This may conceivably be a "dosage" effect (e. g., prednisone, milligram for milligram, is purported to have three to five times the activity of cortisone), or it may possibly be due to the difference in the steroid molecule. In view of the results in case 5, in which both 400 and 200 mg. of cortisone were strikingly ineffective and a small dose of prednisone (30 mg.) highly effective, the "dosage" effect seems unlikely and a difference of effect is probable. Prednisone is an artificially created (i. e., synthetic) material and not naturally produced by the adrenal gland. It may thus have some specific quality making it unusually active against the thrombopenic factor found in that disease. This possibility requires further study, and of course even with the above statements in mind, one cannot rule out completely the possibility that the prednisone molecule acts in a quantitative (i. e., dosage) fashion rather than in a qualitative one.

While in the past we have stressed the difference between "acute" and "chronic" cases of ITP,[1] not only as regards their clinical course but also with respect to their response to therapy, this distinction takes on a different meaning when the results of prednisone therapy are analyzed. The problem may be restated in this fashion: At the time the patient is first examined, the fact that the hemorrhagic symptoms are of short duration (i. e., acute) and apparently never previously present is of little prognostic value in predicting the future course. On the other hand, in young people and children, the appearance of ITP two to three weeks after a well-defined infectious state indicates that the hemor-

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195

rhagic disorder will in most instances clear up spontaneously. Here steroids might still be used to "speed up" a spontaneous type of remission. In all other situations, the response to prednisone could not be correlated with either the acuteness or the chronicity of the hemorrhagic process. Thus, our former belief that the diagnosis of chronic ITP was an almost invariable indication for splenectomy needs modification.

In view of the rather constant effects of prednisone and the increasingly inconstant effects of splenectomy, to say nothing of the fact that the operation of splenectomy presents certain hazards, what should the present program of therapy for ITP be? And what about the future of corticosteroid, more particularly prednisone, therapy?

Largely through the impetus already established by Banti and Micheli for the use of splenectomy in hemolytic anemia, this operation was introduced by Kaznelson [1] in 1916 for the treatment of ITP. For a long time (until about 1950) there was no other form of therapy, and splenectomy was (and still is) being performed in almost all cases of ITP, and even as an emergency procedure in acute cases of the disease.[2] Beginning with 1950, ACTH (and later cortisone) was introduced and found to be of considerable help in reducing the hemorrhagic tendency, probably by a nonspecific effect on blood vessel wall. Later, the transfusion of viable platelets by the use of fresh blood drawn into siliconized bottles or plastic bags proved of considerable value in conjunction with the corticosteroid in tiding the patient over the hemorrhagic crisis. One was still faced, however, with certain cases that failed to respond and with the chronic cases of thrombocytopenia subject to remission and relapse, but always having a low platelet level. In these cases, it was our routine until recently to recommend splenectomy. However, the growing indication that ITP was a "self-perpetuating" immunological disturbance, the often very transient effects of splenectomy in raising the platelet level, and the increasing realization that ITP and systemic lupus erythematosus were closely related led us to consider splenectomy only as a measure of last resort when other measures had failed.

According to the concepts of many present-day workers,[3] ITP may be considered as an "autoimmune" disorder, arising by some obscure antigenic stimulus and attacking the individual's own platelets. In the acute cases, it is conceivable that the antibody develops suddenly, attacks explosively, and often disappears; but in the chronic cases, the immunological mechanism is probably self-perpetuating, thus resulting in chronic thrombocytopenia. The waxing and waning of the thrombocytopenia in a typical chronic case might conceivably result in a temporary rise in platelets in a given case of ITP, but when antibody concentration becomes unusually high, a relapse could occur at a later date. In a previous article,[10] we have pointed to the development of disseminated lupus erythematosus after splenectomy in cases in which latent or "occult" lupus was previously present, and in which only hematological manifestations were present before splenectomy. It seemed possible that removal of the spleen had in some manner aided in dissemination of the lupus process. Since then, we have observed several similar cases, and this observation has been confirmed by others. Further studies indicate that approximately 25% of all patients with apparently typical ITP in whom the spleen is removed will eventually develop systemic lupus. It is apparent that ITP is often a prodrome of the more generalized disease and that the thrombocytopenia, like autoimmune hemolytic anemia or a positive serologic test for syphilis, is as much a manifestation of the disease lupus as the skin lesions or the L.E. test.[11] All of these various considerations, together with the actual end-results of splenectomy, have led us to conclude that ITP is fundamentally a "medical" disorder, in which splenectomy is to be avoided as long as possible, with chief emphasis on treatment by "medical" means, i. e., platelet transfusions and corticosteroids.

Initially we used corticosteroids to reduce the bleeding tendency and to prepare the patient for splenectomy. In the present study, the new steroid prednisone was used, not only to reduce bleeding through its nonspecific effect on blood vessels, but to raise the platelet count and thus perhaps avoid the necessity for splenectomy. Possible avoidance of a major operation is always desirable, especially if this can be done without jeopardizing the individual's life or well-being. On the other hand, there are certain disadvantages to this "medical" form of therapy: 1. The patient must be observed carefully, and some weeks and months are consumed in assaying the effect of prednisone on the platelet count and in adjusting the dose to its proper level. 2. Rounding of the face and other features of hyperadrenocorticism usually develop and may be the occasion for comment by the patient and family. 3. Continued steroid therapy may result in such complications as osteoporosis, hyperglycemia, and a tendency to infections. 4. The patient may conceivably have a cerebral or other important hemorrhage while waiting for the platelet count to rise.

As for the last complication, this did not occur in our present series, and it seems an unlikely event with the patient taking the large starting doses of steroid. The "juggling" of doses and the careful follow-up with frequent platelet counts are difficult

except in the appropriate "setup," but they can be accomplished. The most careful studies are required during the first two weeks. The continued use of relatively large doses of steroid imposes many potential difficulties. Thus, the dose of prednisone was dropped to the lowest possible levels, e. g., 5 to 10 mg. per day as quickly as possible. In most individuals, this amount was sufficient to maintain the platelet level at normal or near normal values. If 15 mg. or 10 mg. can keep the platelet count at 500,000 per cubic millimeter level, 5 mg. or even 2.5 mg. may hold it at one-half normal values, and this is compatible with complete freedom from hemorrhagic manifestations. If an individual requires more than 10 mg. of prednisone per day to keep the platelet level reasonably good, then splenectomy is probably warranted after a period of observation of several months to one year, since the end-results of years of prednisone therapy are unpredictable. It can be stated, however, that many patients with autoimmune hemolytic anemia have tolerated the continued use of relatively small doses of cortisone or prednisone for two to five years without apparent complication.[9a]

It is thus our present intention to continue this nonsurgical method of therapy as long as practicable in order to obtain as full knowledge as we can regarding the value of prednisone and other corticosteroids. Similarly, when assaying the value of ACTH and the corticosteroids in the treatment of autoimmune hemolytic anemia[9a] in which splenectomy had previously been the sole therapeutic method, we performed no splenectomies during a period of three and one-half years. At the end of that time, of 43 cases under observation, a residue of 8 cases was present in which splenectomy seemed to be indicated because of continued hemolysis, poor control with steroid, or complications from steroid therapy. Thus it is our present plan to reserve splenectomy for those cases of ITP that have either failed completely to respond to prednisone or in which the large dosage of prednisone required to keep that patient's condition in remission precludes its continued use. At this time, no predictions can be made as to the ultimate value of prednisone as compared to splenectomy. Nevertheless, it can be stated that the uncertain value of splenectomy in ITP, its possible tendency to disseminate a previously latent lupus, together with the frequency of "spontaneous" remissions and relapses in this probably immunological disease, make it worthwhile to reevaluate conservative "medical" measures as a possible substitute for the more drastic therapeutic method of splenectomy.

Summary and Conclusions

Thirty consecutive cases of idiopathic thrombocytopenic purpura (ITP) were treated with prednisone during a 24-month period. While all cases were of the idiopathic variety, some were acute, some chronic, and some were in relapse after splenectomy. In several cases, previous therapy with ACTH and cortisone or splenectomy had been used, with poor results. The initial dose of prednisone varied between 20 and 150 mg. a day. When the platelet count reached normal levels the dose of prednisone was reduced to "maintenance" levels (2.5-15 mg. a day); this amount was continued for several months and if the platelet level remained normal, prednisone therapy was discontinued. Of the 30 patients, 22 obtained normal platelet counts sometime during the course of prednisone therapy. In the remaining eight, two attained nearly normal platelet levels and two showed a well-defined rise to one-third to one-half of normal values. Four showed little or no rise in platelet levels.

In several patients, thrombocytopenia to a greater or lesser degree returned when prednisone was withdrawn or dosage reduced to low levels. In most instances, however, a second course of prednisone brought about a second remission. It has been possible to discontinue prednisone therapy in 8 of the 22 patients without a drop in their platelet levels, even though a few of these 8 had required a second course of prednisone. Splenectomy was performed in five patients in this series and in only one instance was this followed by a complete and sustained remission. In two patients who had received massive doses of steroids without rise in platelets, splenectomy was followed by a rise in the platelet count to normal, but a gradual drop in the platelet count occurred later in both. In the remaining two cases, splenectomy was followed by prompt relapse in platelet counts, in one case to very low levels. In this patient, another course of prednisone therapy postoperatively resulted in a complete remission. None of the usually mentioned serious complications of corticosteroid therapy were encountered during the 24-month period, although therapy was discontinued in two cases at the patients' requests, one because of mild mood disturbance and the other because she did not like her rounded face.

Prednisone, if given in sufficient dosage, is capable of inducing a normal platelet count in most cases of idiopathic thrombocytopenic purpura, whether acute, chronic, or in relapse after previous splenectomy. Prednisone seems to be more effective in inducing remissions in platelets to normal values than either ACTH or cortisone. The remissions, once established, can usually be maintained by the administration of small doses of the drug (2.5-5 mg. daily). It has become apparent that it is not completely essential to maintain the platelet level at exact normality; complete freedom from all bleeding manifestations can be achieved with the platelet level at one-third to one-half normal values. This

is an important consideration with respect to the use of small doses of prednisone for long-continued therapy. Patients failing to respond to prednisone therapy can undergo splenectomy. The results of splenectomy in ITP, with or without previous prednisone therapy, are always uncertain. It is probable that the relapse rate is at least as great with splenectomy as with prednisone.

In acute and fulminating ITP, the best therapy is prednisone in sufficient dosage, together with fresh blood from plastic bags. Not only may splenectomy be hazardous under such conditions, but a complete remission usually develops with prednisone alone, often persisting indefinitely without further treatment. It has become necessary to re-evaluate splenectomy as a therapeutic measure in ITP. This comes with realization that the disease is subject to long remissions and relapses and that, once having developed, it is often a more or less permanent disturbance. This does not say that permanency necessarily means disability, since many individuals with a slight or even marked reduction in platelets are otherwise quite healthy. Furthermore, the growing realization that ITP is often a prodrome of systemic lupus erythematosus, and that splenectomy may be a factor in the dissemination of occult or latent lupus, has proved another deterrent to our quick use of the operation.

In the treatment of ITP, chief reliance should be placed upon "medical" measures including the use of prednisone and fresh, "plastic bag" transfusions. Splenectomy should be reserved for those severe cases which fail to respond to such measures. In the present day enthusiasm for laboratory tests, too much emphasis has been placed on obtaining complete normality of the platelet count. It is quite evident that patients with ITP can be maintained in full normal activity and without danger of hemorrhage at platelet levels of one-third to one-half of normal. These levels can often be attained by the use of small maintenance doses of prednisone.

Addendum

Since completion of this report, a 60-year-old woman with chronic ITP has not responded to prednisone and has developed marked osteoporosis and partial compression fractures of three vertebrae in four months of prednisone therapy. Recently, two patients with chronic ITP were treated with a new synthetic corticosteroid, triamcinolone (Aristocort). A prompt and striking response in platelet count took place in both cases.

205 Beacon St. (16) (Dr. Dameshek).

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PROGNOSIS IN ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Samuel Silbert, M.D.
and
Herman Zazeela, M.D., New York

Observations of the course of peripheral vascular disease were made in 1,198 patients who satisfied certain criteria as to signs and symptoms. The patients with coexistent diabetes were found to have a 10-year mortality rate of about 38%, compared to 11% for nondiabetic patients. Diabetic patients also had a much higher rate of amputations (34%) than did nondiabetics (8%). Severe hypertension was also associated with some shortening of life expectancy, but its relation to frequency of amputation was complex. The amputation rate was lower in patients who had stopped smoking than in patients who continued to smoke or had never smoked. When acute occlusion of the femoral artery occurred, the prognosis was again much better in the nondiabetic than in the diabetic patients. In a group of 39 patients who underwent sympathectomy no favorable effect on the amputation rate was seen. Peripheral vascular disease in the presence of diabetes calls for rather aggressive measures. In the absence of diabetes, symptoms like intermittent claudication often persist for many years without worsening or even with some alleviation; the condition seems relatively benign, and conservative (nonsurgical) treatment is fairly satisfactory.

The purpose of this study was to determine the prognosis for life and limb in patients with arteriosclerotic peripheral vascular disease and to evaluate certain factors, such as presence of diabetes, use of tobacco, association of hypertension, decade of onset of symptoms, and sex, on prognosis. The cases employed for this investigation were carefully selected from records from the private practice of one of us (S. S.). For this survey, all patients who presented evidence of preceding thrombosis of the coronary or cerebral vessels were excluded, because these conditions in themselves affect prognosis. All patients with uncomplicated arteriosclerotic peripheral vascular disease who had been followed for three years or more after the onset of symptoms and, in addition, all patients who were followed to the time of death or amputation were included. From the large number of records available it was possible to select 1,198 suitable cases of patients seen in the past 15 years. These patients included 942 men and 256 women; there were 958 living and 240 dead; 399 were diabetic and 799 nondiabetic; 353 were hypertensive and 775 normotensive; and 851 were smokers and 214 nonsmokers.

For the purpose of this study the onset of symptoms was regarded as the time of the beginning of the disease, although it is obvious that some degree of vascular disease was certainly present for some time prior to the first symptom. The degree of vascular impairment is shown in table 1. Most of these patients were referred by their personal physicians for opinion, evaluation, and suggestions in regard to treatment. The progress of most of the patients was followed by repeated personal examinations, but, in many, follow-up data was obtained by correspondence with the patient or the referring physician. The symptoms which were regarded as significant of peripheral vascular disease were intermittent claudication, ulceration, or gangrene of the feet.

TABLE 1.—*Degree of Vascular Involvement in 1,198 Patients*

Degree	Involvement: Extent	Patients, No.
5	External iliac, femoral, popliteal, and all foot pulses absent	21
4	Femoral, popliteal, anterior tibial and posterior tibial arteries closed	74
3	Femoral open, popliteal, anterior tibial and posterior tibial arteries closed	581
2	Femoral and popliteal arteries open, anterior tibial and posterior tibial arteries closed	225
1	Femoral, popliteal, and one foot pulse open, one foot pulse closed	201
0	All pulses present, but reduced in size	83

Duration of Life and Cause of Death

Compared with normal persons,[1] patients with arteriosclerotic peripheral vascular disease not complicated by diabetes or severe hypertension showed no shortening of life expectancy (table 2 and fig. 1). Males and females showed no striking difference in this respect. The most striking fact revealed by this study is that patients with diabetes have a much graver prognosis than those free from this disease. For example, the 10-year mortality rate for diabetic patients is about 38%, compared to 11% for nondiabetic patients (table 4). When the patients are divided into groups based on age at onset of the peripheral vascular disease, the life expectancy for the older age group is found to be less than that for the younger groups, as would be expected. In all age groups, the survival curves for nondiabetic patients approximate the normal. Also

in all age groups, the survival curves for diabetic patients show markedly diminished life expectancy. This is most pronounced in the younger groups (fig. 1). The known cause of death in the majority of cases was either coronary thrombosis (42%) or cerebral thrombosis (12%). The presence of moderate hypertension (blood pressure below 200/110 mm. Hg) made no alteration in mortality figures. Severe hypertension (blood pressure over 200/110 mm. Hg) caused some shortening of life expectancy (table 3 and fig. 2). For those patients accustomed to smoke who stopped smoking, the mortality rate is about one-half that for patients who continued to smoke (fig. 3). Nonsmokers, however, showed a mortality rate as high as that of smokers. Apparently, in this group other factors, possibly hereditary, are more important.

TABLE 2.—*Comparative Mortality Rates for Nondiabetic and Diabetic Patients with Arteriosclerotic Peripheral Vascular Disease By Years of Follow-up Per Total Patients in Study*

Period of Follow-up, Yr.	Nondiabetic Male Total	Nondiabetic Male Died No.	Nondiabetic Male Died %	Nondiabetic Female Total	Nondiabetic Female Died No.	Nondiabetic Female Died %	Diabetic Male Total	Diabetic Male Died No.	Diabetic Male Died %	Diabetic Female Total	Diabetic Female Died No.	Diabetic Female Died %
3.....	681	9	1.3	118	2	1.7	261	12	4.8	138	4	2.9
5.....	627	18	2.9	106	4	3.8	222	28	12.1	119	8	6.7
10.....	491	57	11.6	83	9	10.8	185	68	36.8	90	36	40
15.....	233	75	32.2	30	13	43.4	133	85	63.8	55	44	80
20.....	112	79	64.7	18	13	72.2	109	96	88.1	48	44	91.6
30.....	94	83	88.2	14	13	92.9	101	99	98	46	45	97.8

TABLE 3.—*Effect of Hypertension on Survival Rates* for Patients With and Without Diabetes*

Blood Pressure	Period of Follow-up, Yr.	Nondiabetic Patients Living No.	Nondiabetic Patients Died No.	Nondiabetic Patients Died %	Diabetic Patients Living No.	Diabetic Patients Died No.	Diabetic Patients Died %
Normal	3	506	7	1	148	8	5
	5	463	15	3	126	17	12
	10	351	46	11	80	52	39
	15	121	60	33	25	69	73
	20	33	66	66	7	79	92
Under 200/110 mm. Hg.	3	98	2	2	52	6	10
	5	86	3	3	37	10	21
	10	60	7	10	29	23	44
	15	19	10	34	10	27	73
	20	5	10	66	2	30	94
Over 200/110 mm. Hg. ..	3	78	2	2	33	2	6
	5	71	4	5	28	7	20
	10	55	13	18	13	20	60
	15	22	17	44	4	22	85
	20	7	19	73	1	22	96

* Combined rates for men and women.

The observation that only 8% of 800 nondiabetic patients who were treated by nonsurgical methods required amputation is particularly valuable. This serves as a control group for comparison with patients treated by sympathectomy or arterial grafts. It indicates that nonsurgical treatment is fairly satisfactory for preservation of extremities in this group. It is unlikely that the results of surgical treatment can show an impressive improvement over these figures. In the diabetic patient, on the other hand, the results of medical treatment are obviously poor. A total of 34% of these patients suffered amputations of one or both legs. It is in

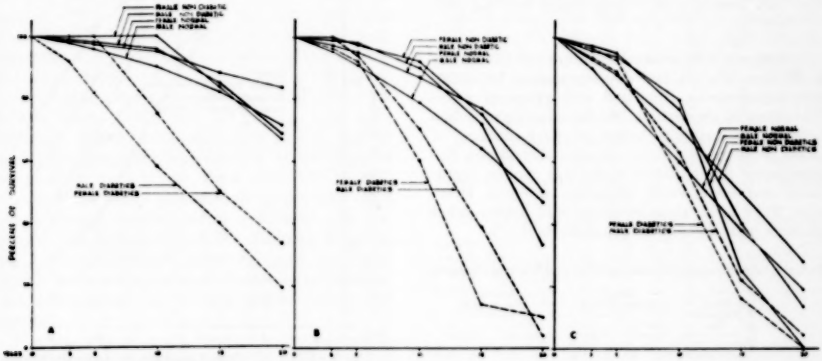

Fig. 1.—Survival curves for patients with arteriosclerotic vascular disease with and without diabetes. *A*, age group 40-50; *B*, age group 50-60; *C*, age group 60-70.

Necessity for Amputation

As in the statistics for life expectancy, the most striking observation resulting from this study was the graver prognosis for diabetic compared with nondiabetic patients (table 4). Thus, in 799 nondiabetic patients there were only 64 amputations (8%), while in 399 diabetic patients there were 137 amputations (34%). The amputation rate in female patients is appreciably higher than that in male patients.

this group that more aggressive treatment is needed. Comparative, carefully documented results in a group of diabetic patients treated by sympathectomy and/or arterial grafts will be awaited with interest. Up to now, no such report has come to our attention.

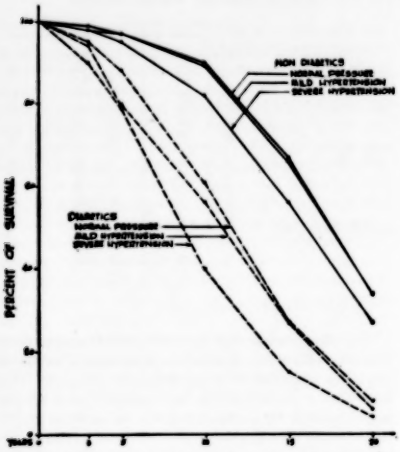

Fig. 2.—Effect of hypertension on mortality rates for patients with arteriosclerotic vascular disease with and without diabetes.

In patients with severe impairment of circulation in the legs, the gradual development of hypertension is sometimes associated with progressive improvement in circulation. On the other hand, when hypertensive patients suffer a sharp decline of blood pressure due to a coronary thrombosis, the impairment of circulation in the legs may be aggravated and occasionally gangrene develops. However, there is no clear evidence that hypertension protects patients from amputation (table 5).

TABLE 4.—*Amputations in Patients With and Without Diabetes*

	Total Patients, No.		Single Amputations				Double Amputations			
			Non-diabetic		Diabetic		Non-diabetic		Diabetic	
	Nondiabetic	Diabetic	No.	%*	No.	%†	No.	%*	No.	%†
Male	681	261	50	7	76	29	1	0.1	12	5
Female	118	138	14	11	61	44	2	2.0	12	9
Total	799	399	64	8	137	34	3	0.4	24	6

* Per cent of nondiabetic patients.
† Per cent of diabetic patients.

The continued use of tobacco results in a higher rate of amputations than when tobacco smoking is stopped (table 6). This is more clearly seen in the nondiabetic patients, in whom the amputation rate is 5% in former smokers and 10% in those who continued to smoke. In the diabetic patients, the overshadowing effect of this disease seems to obscure the harmful effects of smoking. However, in

TABLE 5.—*Effect of Hypertension and Sex on Amputations*

	Nondiabetic Patients			Diabetic Patients		
	Male	Female	Total	Male	Female	Total
Blood pressure normal						
Cases, no.	524	42	566	178	51	229
Amp., no.	28	5	33	47	24	71
Amp., %	5	12	6	26	47	31
Moderate hypertension						
Cases, no.	84	33	117	44	38	82
Amp., no.	10	4	14	13	12	25
Amp., %	12	12	12	30	32	30
Severe hypertension						
Cases, no	56	44	100	11	40	54
Amp., no.	2	4	6	4	18	22
Amp., %	4	10	6	29	45	41
Blood pressure not recorded	...	...	11	...	...	19
Total amputations			64			137

those patients who have never smoked the amputation rate is as high as in those who continued to smoke. In this group it appears that other factors, such as heredity and diet, play a more important role.

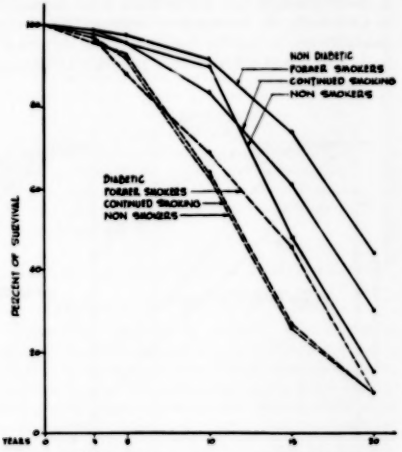

Fig. 3.—Effect of tobacco smoking on mortality rates for patients with arteriosclerotic vascular disease with and without diabetes.

Our studies indicate that the percentage of amputations in patients with iliac artery occlusion is higher than in those with less extensive disease (table 7). The graver outlook for patients with diabetes in this group is apparent. For example, in 69 nondiabetic patients there were 11 amputations

(16%), while in 26 diabetic patients there were 12 amputations (46%). Severe impairment occurred in 95 cases with 23 amputations (24%). Less severe impairment occurred in 1,103 cases with 178 amputations (16%). Amputations are thus more frequently required in more advanced cases.

TABLE 6.—*Effect of Smoking on Amputations*

	Nondiabetic Patients			Diabetic Patients		
	Male	Female	Total	Male	Female	Total
Nonsmokers						
Cases, no.	37	53	90	30	90	124
Amp., no.	3	9	12	11	37	48
Amp., %	8	17	10	37	39	39
Former smokers						
Cases, no.	355	32	387	105	12	117
Amp., no.	18	3	21	30	4	34
Amp., %	5	9	5	29	33	29
Continued smoking						
Cases, no.	231	21	252	87	8	95
Amp., no.	24	0	24	18	3	21
Amp., %	10	0	10	21	38	22
Not recorded	...	...	7	...	...	34
Total			64			137

Prognosis in the Acute Femoral Occlusion Syndrome

Sudden occlusion of a femoral artery occurs quite frequently in the course of peripheral vascular disease. At times, it may be the presenting complaint and the first indication to the patient of circulatory trouble. The diagnosis is easily made. Usually there is a history of sudden onset of severe pain in a lower extremity after walking a short distance and at times pain or numbness in the foot at rest. The patient will usually note that the foot is pale and cold. On examination, in addition to the pale, cold extremity there will be an absence of all arterial pulsations below the femoral. The oscillometric readings below the knee will be markedly reduced. In this series, there were 123 patients who were examined shortly after the acute closure and in whom the diagnosis was obvious at the time of examination. In addition, there were 144 patients in whom the acute closure had apparently taken place several months before. Although the extremity was no longer cold, the diagnosis could be made with reasonable certainty from the fairly typical history, the reduced oscillometric readings, and the absence of arterial pulses below the femoral.

The majority of acute femoral artery occlusions take place at the lower end of Hunter's canal where the artery passes through an opening in the adductor magnus muscle to enter the popliteal space. Twenty-five per cent of the patients in this series presented evidence of acute occlusion at this site. The other frequent location of acute closure is at the brim of the pelvis where the external iliac artery passes beneath Poupart's ligament to become the femoral artery. At these points, unusual strain or pressure is exerted in the femoral artery. The presence of disease in the intima would make the artery more susceptible to thrombosis at these locations.

It is noteworthy that major amputation was necessary in only 48 of the 267 patients who had acute femoral artery occlusions (18%). There were 185 nondiabetic patients with 22 amputations (12%) and 82 diabetic patients with 26 amputations (32%).

The graver prognosis for diabetic patients is again evident. In this group more aggressive treatment is obviously needed. Patients with acute femoral artery thrombosis are likely to show patent arteries below the level of occlusion, particularly if studied with arteriograms shortly after the acute episode. There is a reasonable possibility that prompt insertion of a graft or bypass could save many of these extremities.

In the nondiabetic patient, slow, gradual recovery is the usual rule in patients who develop this type of acute vascular accident. The severity of the intermittent claudication gradually diminishes and may disappear completely. The extremity usually becomes warm, oscillometric readings gradually improve, and pulsations occasionally reappear in the foot.

Value of Sympathectomy in Prevention of Amputations

In the present series of 1,198 cases, in only 39 had sympathectomy been done. This group is too small to be statistically valuable. In 22 nondiabetic patients there were four amputations (18%), while in 17 diabetic patients there were eight amputations (47%). This makes a total of 12 amputations (31%), as compared to 16% in the entire series of 1,198 cases. In this small group sympathectomy had no favorable effect on amputation rate.

It is of great importance to establish whether or not sympathectomy has any prophylactic value in preventing amputations. Up to now no reliable statistics on this point have been published. We have established that 30% of diabetic patients who have one leg amputated will lose the second leg within three years and 51% within five years.[2] This is a control group and may be compared to a group of diabetic patients in whom there is necessity for amputation of the second leg after prophylactic sympathectomy. It would be desirable for every

TABLE 7.—*Effect of Severity of Disease on Amputation Rate*

Severity		0	1	2	3	4	5	Total
Nondiabetics	Cases, no.	76	155	121	378	48	21	799
	Amp., no.	1	2	13	37	10	1	64
	Amp., %	1	1	10	10	20	5	8
Diabetics	Cases, no.	7	46	114	206	36	0	399
	Amp., no.	0	8	39	78	12	0	137
	Amp., %	0	17	34	38	46	0	34
Total	Cases, no.	83	201	235	584	74	21	1198
	Amp., no.	1	10	52	115	22	1	201
	Amp., %	1	5	22	20	30	5	17

diabetic patient who requires amputation of a leg to have a sympathectomy on the remaining leg and to be followed to determine if a second amputation was necessary. If the percentage of second amputations required after prophylactic sympathectomy was appreciably less than 30% in three years or 51% in five years, the value of this procedure would be objectively established. An even more critical evaluation would result if such a study was made on an alternate case series within the same hospital service.

Effect of Various Factors on Progress

Of the 1,198 patients, 83 were seen only once and the results of treatment in this group are undetermined. A total of 201 cases ended in amputation, and these are obvious failures. Of the remaining 914 patients, 366 improved, in 264 the disease remained stationary, and 284 became worse (table 8).

Patients were regarded as improved if they reported that the distance they could walk without pain was appreciably greater. We are aware that increased walking distance without pain serves only as a crude index of improved circulation. However, since the purpose of this study was to determine the effect of various factors on progress and since the same criteria were used for each group, it has some value as a means of comparison.

Patients with ulcerations or gangrene which healed completely were also regarded as improved. Those who showed objective evidence of increased blood flow by return of pulsations or increased oscillometric readings likewise were included in this group. A few patients reported no improvement in symptoms but there was clear objective evidence of better circulation. These also are included in the improved group.

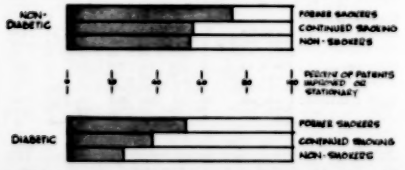

Fig. 4.—Influence of smoking on improvement of circulation for patients with and without diabetes.

It is important to stress that patients who are classified as having stationary disease may not be seriously disabled. The chief complaint in most patients with arteriosclerotic peripheral vascular disease is intermittent claudication. This is not a seriously disabling condition for most individuals, and it is rarely necessary for these patients to stop work or even change their occupation. They are usually completely comfortable at rest or while standing, and can walk variable distances without discomfort. Transportation facilities usually carry such individuals close to their places of employment or homes, and their limited ability to walk is no great handicap. The distance they can walk without pain may remain constant for many years. The improved and the stationary patients may be combined as the "favorable" group, in contrast to those who became worse.

Separation of these patients into those with and without diabetes again shows the graver prognosis in the diabetic patient. Of 757 nondiabetic patients, 496 improved or remained unchanged (66%); of 358 diabetic patients, 134 improved or remained unchanged (37%) (table 8).

The harmful effect of the use of tobacco on progress is apparent in table 8 and figure 4. The percentage of improved cases in those patients who stopped smoking is about double the figure for those who continued smoking. The percentage of improved cases is least in those patients who have never smoked and again indicates that other factors, possibly diet or hereditary disposition, are more important in this group.

Table 8.—*Effect of Diabetes and Use of Tobacco on Progress of Disease*

	Nondiabetic Patients (799 Total)					Diabetic Patients (399 Total)				
	Total	Non-smokers	Stopped Smoking	Continued Smoking	Not Recorded	Total	Non-smokers	Stopped Smoking	Continued Smoking	Not Recorded
Seen only once	42	0	4	36	2	41	17	15	6	3
Improved, no.	360	91	188	69	78	66	12	34	14	6
%		27	49	28			11	31	16	
Stationary, no.	196	25	91	60	20	68	15	24	20	9
%		28	24	28			14	22	22	
Worse, no.	261	41	104	96	20	224	84	53	56	31
%		45	27	44			75	47	62	
Total valid, no.	699	90	283	216		312	111	111	90	

Table 9.—*Effect of Hypertension on Progress of Disease in Male Nondiabetic Patients*

	Normal Blood pressure	Moderate Hypertension	Severe Hypertension
Improved, no.	220	27	17
%	43	35	34
Stationary, no.	130	19	9
%	25	24	18
Worse, no.	165	32	24
%	32	41	48
Total	515	78	50

The effect of hypertension on progress is shown in table 9. It is apparent that hypertension is a harmful complication. Unfavorable progress is noted in 32% of patients with normal blood pressure, 41% with moderate hypertension, and 48% with severe hypertension.

Summary

The life expectancy of patients with uncomplicated arteriosclerotic peripheral vascular disease is not shortened, compared with normal individuals. Eleven per cent of these patients die within 10 years and 33% within 15 years from onset of symptoms. The prognosis in the disease complicated by diabetes is much graver. In this study, 38% of the diabetic patients died in 10 years and 69% died in 15 years from the onset. Moderate hypertension has no influence on life expectancy, but severe hypertension has an unfavorable influence. The continued use of tobacco by smokers shortens life expectancy.

Amputations are infrequently necessary in patients with the disease who do not have diabetes. Diabetic patients require amputation four times as frequently as those without this disease. The amputation rate in females is appreciably higher than that in males. The continued use of tobacco increases the percentage of those who require amputation. The presence of hypertension does not affect amputation rate.

Acute femoral artery thrombosis is usually a relatively benign vascular accident in nondiabetic patients, and amputations are necessary in only 12%. In the patients with diabetes the amputation rate is 32%. On conservative management, 66% of nondiabetic patients improve or the disease becomes stationary. Of patients with diabetes, only 37% respond in a favorable manner.

In general, this study indicates that conservative (nonsurgical) management of patients with arteriosclerotic peripheral vascular disease is fairly satisfactory in the nondiabetic patient but that the results in the diabetic patient are poor. More aggressive measures are necessary in this group. It remains to be shown whether or not sympathectomy or vascular grafting procedures will improve the long-term results in this group.

1126 Park Ave. (28) (Dr. Silbert).

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MEDICOLEGAL ASPECTS OF INTUBATION GRANULOMA

Richard T. Barton, M.D., Beverly Hills, Calif.

The fact that laryngeal granuloma may occasionally occur as a sequel to endotracheal intubation in no way invalidates the many advantages of this anesthetic technique.[1] On the contrary, the technique is being employed more widely than ever because of the protection it affords against aspiration, hypoxia, and laryngospasm.[2] Nevertheless, claims of negligence and resultant law suits are not uncommon, even when the patient has made a complete recovery from such a postintubation granuloma. The material herein is based on personal experience as a consultant and expert witness in such cases.

Etiology

Jackson [3] has demonstrated that the initial lesion in laryngeal granuloma is a contact ulcer caused by the endotracheal tube moving on the thin mucosal surface overlying the vocal processes of the true cords. In certain instances, trauma of this type is almost impossible to avoid in spite of the various present-day techniques with use of thiopental (Pentothal) sodium and succinylcholine (Anectine) chloride. This may occur at the time the tube is

Associate Consultant in Otolaryngology, University of California, Los Angeles

Endotracheal intubation has sometimes been followed by laryngeal granuloma in spite of the best prophylactic measures. This occurrence does not necessarily reflect unfavorably upon the anesthesiologist. Two cases here cited show that some patients tolerate an endotracheal tube for days without evidence of trauma to the larynx while others after a brief period of intubation develop granulomatous lesions with persistent aphonia or dysphonia. These lesions, initially sessile, generally become pedunculated and are eventually ejected. The period of vocal disability is important to patients who use their voices occupationally. Recovery is not hastened by cauterizing the granulation tissue. The anesthesiologist can forestall litigation in some patients either by avoiding endotracheal intubation or by explaining to the patient in advance that granulomas do not mean negligence.

passed or during the anesthetization. Figure 1, taken from a previous report,[4] illustrates the difference between the position in the glottis of the tube during general anesthesia (fig. 1, *B*) and of the bronchoscope during local anesthesia (fig. 1, *A*). This serves to dramatize the difficulty in avoiding the pincer-like movements of the vocal processes on the tube and the resulting abrasion when the swallowing reflex is still partly present, as in most

Fig. 1.—*A*, diagram showing bronchoscope in glottic chink during local anesthesia, as visualized from above. Tube can be seen against anterior commissure remote from vocal processes. *B*, diagram showing endotracheal tube in glottic chink, during general anesthesia, as visualized from above. Tube can be seen against posterior commissure pinched by vocal processes. (Reproduced with permission from *New England Journal of Medicine*.[4])

instances of thiopental anesthesia. The following case is an interesting clinical example, however, of a prolonged intubation without such damage.

Case 1.—A 73-year-old male underwent a craniotomy on Dec. 22, 1947, which resulted in the loss of consciousness, a left hemiplegia, and a partial pharyngeal paralysis. An inoperable malignant tumor was found at surgery. Because the patient was "drowning in his own secretions" and suctioning appeared inadequate, an endotracheal tube was passed as a temporary expedient, inasmuch as the patient was not expected to live more than a few days. This intubation was performed without the use of anesthesia by Dr. Warren Greene at 11 a.m. on Dec. 23, 1947.

The patient tolerated the airway well, even though semicomatose. He made some feeble attempts at phonation and swallowing, and there were occasional movements of the head and neck. The conditions closely simulated those of an intubation with the patient under general anesthesia rather than a bronchoscopy with the patient under local anesthesia. At 4 a.m. on Jan. 2, 1948, the patient died.

This, so far as can be determined, is the longest such intubation in the medical literature. Yet at autopsy the larynx was free of evidence of trauma (fig. 2).

This case demonstrates that, under the ideal conditions of gentle introduction of the tube, a minimum of extralaryngeal movements of the neck, and the avoidance of the "laryngeal pincer," a patient may well tolerate endotracheal intubation for a long time. Unfortunately, these ideal conditions cannot always be achieved at the time of surgery.

Treatment

The prophylaxis of laryngeal granuloma is discussed more thoroughly in an earlier paper,[4] and the reader is referred to it for lack of space herein. The point is, however, that in spite of all measures of prophylaxis against laryngeal granuloma, the lesion may unavoidably occur even under the best of conditions, and this occurrence does not necessarily reflect unfavorably on the anesthesiologist.

One of the commonest causes of litigation in these instances is unwise management of the granuloma. Many patients with granuloma are subjected to repeated operations—direct laryngoscopy, suspension laryngoscopy, and even thyrotomy. As a consequence of having experienced much discomfort and expense, the patient feels he deserves some compensation.

Baron and Kohlmoos [5] have stated that removal is not required unless the granuloma interferes with respiration and phonation. This is undoubtedly more effective treatment than the repeated attempts at removal described by others.[6] Surgical removal is most likely to be successful when the lesion has reached the pedunculated stage, and attempts at removal during the sessile stage should be avoided, as recurrence is likely. However, as I have shown in a previous study,[4] the eventual outcome after a well-defined pedicle has developed is a self-amputation. Therefore, except where there is serious dyspnea, the treatment of choice is strict voice rest without surgery; the polyp will eventually be ejected. The following is an illustrative case.

Case 2.—A 51-year-old female underwent a radical mastectomy in February, 1953, under endotracheal anesthesia. She noticed a loss of voice immediately upon recovery of consciousness. Her surgeon ordered steam inhalations and antibiotics, but this treatment was without benefit. The anesthesiologist never saw the patient after the surgery, and one month after the operation a laryngologist was called in

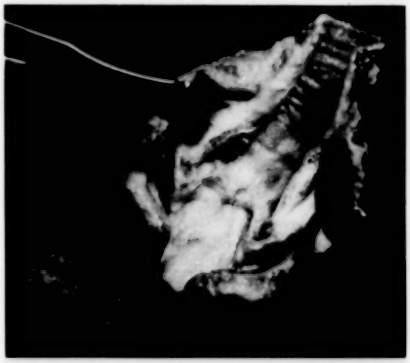

Fig. 2.—Larynx removed at autopsy after endotracheal tube was in place for 8 days and 17 hours. Note lack of macroscopic injury.

consultation because of the persistent aphonia. During the next year the patient underwent laryngoscopy and removal of laryngeal granulomas on three occasions and finally a thyrotomy. All procedures failed. Cortisone therapy was tried, as well as cauterization of the granulation tissue. The granuloma flourished instead.

The patient was first seen by me on March 23, 1954, and found to have a 1-cm. spherical mass of granulations on both vocal processes. The patient was forbidden to

speak or whisper but permitted only to use a pad and pencil. An antitussive was prescribed. On May 10, 1954, the sessile masses were seen to have developed a definite pedicle bilaterally. On July 26, 1954, the left cordal mass was gone and the cord appeared normal. The voice had improved too. On Nov. 18, 1954, the cords were both clear. The patient remembered coughing up a "small raspberry-like mass," and her voice was again normal. There has been no recurrence.

Nevertheless, the patient sued the anesthesiologist, contending he neglected her by not seeing her postoperatively despite the fact that he admitted difficulty in intubating her at the time of surgery. I was unable to dissuade her from the legal action, inasmuch as she felt that "Dr. ..... should pay for all the hospital days and surgical discomfort he caused me." The anesthesiologist won the case.

The anesthetist can protect himself against lawsuit by close postoperative follow-up. Hoarseness, dysphonia, or persistent sore throat should be a signal to the anesthesiologist to obtain the consultation of a laryngologist immediately. A not uncommon complaint brought against the physician-anesthetist is that he failed to see the plaintiff postoperatively and thereby neglected the patient, as described in case 2.

It is admittedly difficult for the anesthesiologist to follow the patient's condition after surgery in many instances. For example, the patient may be discharged by the surgeon from the hospital the following day, before the busy anesthetist can see him. Furthermore, the granulomas may take one or two weeks to develop, and the patient by this time may be out of the anesthetist's reach. However, as Roman [7] has stated, "the responsibility of the anesthesiologist does not terminate when the anesthetic mask is removed from the patient's face or when the needle is withdrawn from a vein or the intrathecal space. . . . It seems obvious that the responsibility of the physician administering these drugs should not end until the actions of the drugs are terminated and until the complications that may arise from such administration have been obviated or properly treated."

Before the surgery, the anesthetist should note whether the patient is a singer or uses his voice professionally and whether the patient has had previous laryngeal surgery, and he should be prepared for those patients in whom intubation might be difficult. The following case is an example of such "lawsuit prophylaxis."

CASE 3.—A 60-year-old male popular singer had a singer's node removed by me while he was under thiopental-succinylcholine anesthesia. He made an excellent recovery but sued his radio employers, claiming they had forced him to overwork his voice and that the overwork produced the singer's node. The man was obviously litigation-minded. A number of years later the patient entered the hospital for abdominal surgery and demanded "Pentothal anesthesia." The anesthesiologist felt that an endotracheal tube would be necessary with this anesthetic technique during abdominal surgery and was wisely reluctant to pass an endotracheal tube in view of the history of laryngeal surgery. It was therefore the advice of all of us concerned that a spinal anesthetic be given. Any real or imagined injury to this singer's vocal cords was thereby avoided, as well as a possible lawsuit.

Summary

Most, if not all, the litigation over laryngeal granulomas due to intubation could be avoided if the following policies were adopted. First, the anesthesiologist should see the patient preoperatively and postoperatively—preoperatively to appraise the patient and postoperatively to discuss the complications if present. Second, if the anesthetist is no longer following the case, the surgeon should watch for laryngeal granuloma and seek consultation. Third, the laryngologist can aid by judicious treatment and by explaining to the patient that granulomas do not mean negligence.

9730 Wilshire Blvd.

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THE PARENTS OF SCHIZOPHRENIC PATIENTS.—One rapidly realizes that these parents are struggling with their own problems and defenses and, with very rare exceptions, have striven to do their best for their children within their abilities and the limits placed by their own emotional difficulties. Too often the psychiatrist forgets his psychiatric understandings when dealing with parents and expects them to have been able to be different from what they were, or to change through reading a book or just because he tells them to behave differently. They, too, are as much bound to their unconscious conflicts as the patients and could not have been other than they were.—T. Lidz, A. R. Cornelison, S. Fleck, and D. Terry, The Father, *Psychiatry*, November, 1957.

ANESTHESIA FOR ADRENALECTOMY

CLINICAL REPORT ON FIFTY-FOUR PROCEDURES

Barnett J. Junker, M.D., William S. Derrick, M.D., Nylene Eckles, M.D.
and
Edgar C. White, M.D., Houston, Texas

The histories of 41 patients who had undergone adrenalectomy were reviewed with respect to the relative advantages of the various types of anesthesia used at operation. The positioning of the patient precluded the possibility of satisfactory spinal anesthesia. The most frequent procedure consisted of premedication with pentobarbital, meperidine, and atropine, induction with intravenously given thiopental sodium and tubocurarine, and endotracheal administration of nitrous oxide, oxygen, and ether. Although four hypotensive episodes occurred, there were no surgical or anesthetic deaths. This good result is ascribed to a careful program of steroid replacement therapy involving the preoperative use of cortisone acetate, the availability of hydrocortisone in both operating and recovery room for use if hypotension developed, and the use of cortisone in the recovery room and throughout the postoperative life of the patient.

In the recent medical literature, there are numerous reports of adrenal surgery for hypertension and adrenal cortical hyperfunction (Cushing's disease). There are a number of reports which describe the results of bilateral adrenalectomy as a palliative procedure in advanced metastatic malignant disease, and this procedure is being carried out with increasing frequency in the management of metastatic breast cancer. The dramatic reversal in some cases of the osteolytic destruction of bone, as well as soft-tissue metastases, gives the procedure a useful place in surgery. Huggins and Dao,[1] in a series of 100 cases, reported an operative mortality of only 5%, and it is now generally agreed that bilateral adrenalectomy is a reasonably safe surgical procedure.[2]

The fact that a review of the literature shows no common agreement as to the use of anesthetic agents or techniques and that most of the articles on adrenalectomy make no reference, or only a passing reference, to anesthesia is of interest. Accordingly, a review of 54 adrenalectomies done between October, 1954, and January, 1957, at the University of Texas M. D. Anderson Hospital and Tumor Institute is presented with a view toward evaluating the safety of the anesthetic agents and techniques used, as well as the preoperative and postoperative regimen of steroid replacement. Forty-one patients, representing 54 operative procedures, are included in this study. Twenty-two had bilateral adrenalectomies done as a one-stage procedure. Thirteen had bilateral adrenalectomies done in two stages. The interval between stages varied from 5 to 26 days.

Sex of Patients

There were 39 women in this series, of whom 35 had carcinoma of the breast. Two had adrenal cortical hyperfunction, and one had malignant melanoma. Of the two men in the series, one had been given a diagnosis of primary carcinoma of the adrenal and the other a diagnosis of adrenal cortical hyperfunction.

Preoperative Medical Survey

The preoperative understanding of the patients, psychologically as well as clinically, is an important factor in their preparation for surgery. Clinical evaluation of these cases has included a complete history and physical examination and complete roentgenographic bone and chest survey to determine the extent of the metastatic disease. Cardiac evaluation included electrocardiography. Hematological studies included a complete blood cell count and hematocrit determination. Blood chemistry studies included determinations of the albumin-globulin ratio, prothrombin time, and fasting blood sugar, total protein, and blood urea nitrogen levels. Examination of the urine was also performed. Deficiencies were corrected. These patients may present many problems, including pleural effusion, metastatic pulmonary disease, liver metastases, reduced platelet counts due to bone marrow metastases, and cerebral metastases.

Preoperative Evaluation and Medication

A medical evaluation, including a complete physical examination, blood cell count, urinalysis, electrocardiogram, and roentgenograms as indicated, was done by a staff internist who had been seeing the patient and who also managed the preoperative and postoperative steroid replacement therapy. An estimate was made of the surgical risk. If the patient was anemic, blood transfusions were given pre-

From the University of Texas M. D. Anderson Hospital and Tumor Institute.

operatively, and blood was always available at the time of surgery. An anesthesiologist saw the patient the day before surgery and ordered the preoperative medicaments with the exception of cortisone, which was prescribed by the staff internist who had been seeing the patient in the clinic and who was to follow the case postoperatively.

Preoperatively given medicaments included pentobarbital (Nembutal), 100 mg., administered at bedtime and again two hours before surgery, and meperidine (Demerol) hydrochloride, 50 mg., and atropine, 0.3 mg., given one hour before starting anesthetization. The program of preoperative cortisone medication consisted of cortisone acetate, 50 mg., given orally at 6 p. m. and 12 midnight the night before surgery, and cortisone acetate, 150 mg., injected intramuscularly one hour before operation. A 100-mg. ampul of hydrocortisone was sent with the patient to the operating room and to the recovery room for intravenous use if hypotension developed. Orders were written preoperatively to add 100 mg. of hydrocortisone to 1,000 cc. of 5% dextrose and to give 100 cc. (10 mg.) in a period of 15 minutes if the systolic blood pressure fell to 90 mm. Hg or below; this was followed by the administration of 100 cc. per hour.

Choice of Anesthesia

Spinal anesthesia was not used in this series because the lateral positioning (a modified kidney position) would be uncomfortable to the patient. The possibility that the pleura might be inadvertently opened during surgery, which usually involved resection of the 11th rib, also had to be considered. General anesthesia by the endotracheal route was chosen, therefore, as a matter of comfort to the patient; it also better enabled the anesthetist to cope with the possibility of open-chest surgery and to secure adequate ventilation of the patient.

Anesthetic Management

Vital signs were checked and recorded; the intravenous administration of either 5% dextrose or isotonic sodium chloride solution was started with either an 18-gauge needle or a Rochester plastic needle; and anesthesia was then induced in all patients with a 2.5% solution of thiopental (Pentothal) sodium given in minimal intermittent doses. In 52 of the 54 procedures, the patients were given thiopental, nitrous oxide and oxygen, ether, and tubocurarine and intubated orally with a cuffed endotracheal tube. Anesthesia was then carried on with ether, with intermittent doses of tubocurarine as indicated. The other two patients were also intubated and anesthesia continued with thiopental, nitrous oxide and oxygen, and succinylcholine drip (0.2%).

Most patients were placed in a modified kidney position, which decreased ventilation. All had assisted respiration. An Emerson or a Jefferson pulmonary ventilator was used in 23 of the 54 procedures. The respirations of the remaining patients were assisted by hand. Fifteen different nurse anesthetists, anesthesiology residents, or staff anesthesiologists administered the anesthetic in these 54 instances. There were no deaths due to anesthesia in this series.

One patient, who had a previous history of convulsions, died suddenly on the fourth postoperative day. Death was interpreted to be on the basis of cerebral metastases. Hypotensive episodes occurred in four patients. One occurred during a preliminary tracheostomy done with local anesthesia. This was being done because of recurrence of a lesion in the neck involving the recurrent laryngeal nerve. When the blood pressure dropped to 80 mm. Hg systolic, surgery was canceled, and the procedure was done later, without difficulty, in two stages, with the patient under endotracheal anesthesia via the tracheostomy. Another transient episode occurred during turning of the patient, but the patient did not require any treatment. In a third episode the patient responded to 100 mg. of hydrocortisone given intravenously. The last episode occurred in the recovery room, and the patient also responded to hydrocortisone administered by intravenous drip. This last patient had cerebral metastases and died 15 days later. Transient drops in systolic blood pressure from 10 to 65 mm. Hg were recorded, usually during induction of anesthesia or upon turning of the patient from one lateral position to the other, and were treated, with the above exceptions, by lightening of anesthesia or by blood replacement.

Fluids and Blood Replacement

All except one of the patients (with adrenal cortical hyperfunction) received from one to three units of blood during their surgical procedures in addition to 5% dextrose and isotonic sodium chloride solution, the amounts varying with the length of surgery. Anesthesia time varied from 40 minutes to 6 hours and 10 minutes, with 34 of the 54 procedures lasting more than 3 hours.

Postoperative Administration of Cortisone

On arrival in the recovery room, the patient was given cortisone, 50 mg., intramuscularly and put on maintenance therapy with 50 mg. every four hours the first day, 50 mg. every six hours the second day, 25 mg. every four hours the third day, 25 mg. every four hours the fourth day, 25 mg. every four hours the fifth day, and 12.5 mg. every four hours the sixth day; dosage on discharge was 25 mg. of cortisone twice a day. This program was varied according to the response and needs of the patient. The cortisone dosage for maintenance on an outpatient basis was likewise varied according to the patient's need and must be continued for the duration of life.

Summary

The records of 41 patients having a total of 54 procedures for adrenalectomy at the University of Texas M. D. Anderson Hospital and Tumor Institute between October, 1954, and January, 1957, were reviewed. Endotracheal administration of nitrous oxide, oxygen, and ether and the use of thiopental (Pentothal) sodium, tubocurarine, and assisted respiration constituted the procedure in 52 of these procedures. Although four hypotensive episodes occurred, there were no operative or anesthetic deaths. Management of preoperative and postoperative steroid replacement therapy by a staff internist, as well as adequate preoperative and postoperative preparation and evaluation of the patients, contributed materially to the safety of the procedure.

6723 Bertner Ave. (25) (Dr. Derrick).

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RADIATION HAZARDS OF INTRAVENOUS PYELOGRAPHY

Irving Van Woert Jr., M.D., Paul I. Kearney, M.D., Ilhan Kilicozlu, M.D.
and
John F. Roach, M.D., Albany, N. Y.

In an investigation of the possibility of gonadal injury by x-rays, a preliminary study was made of the records of 200 consecutive patients who had undergone intravenous pyelography. The evidence, in retrospect, showed that about 75% of the pyelograms had been justified, and that close adherence to indications could have eliminated about one-fourth. Measurements were made to determine the amount of radiation received by testes or ovaries during intravenous pyelography. In adults, the dose received was generally less than one roentgen for the ovaries and more, up to several roentgens, for the testes. A critical study of the information gained from 4,000 intravenous pyelograms, with films exposed at 5, 10, and 15 minutes after injection of the opaque medium, showed that the first two exposures might well be limited to the renal area since not one instance was found in which they gave information vital to the diagnosis of lower ureteral disease. A piece of lead or lead rubber should be used to cover the testes in the male patient and to shield the lower half of the abdomen in the female patient against undesired radiation, and actual exposure should be reduced to the minimum by strictly observing the indications and relying on the 15-minute or subsequent films for information as to the ureters.

Recent work has indicated the possibility that young patients (children and young adults) are receiving radiation to their gonadal regions, during the course of diagnostic x-ray studies, that may have undesirable effects manifest in future offspring. Of all the common x-ray examinations, intravenous pyelography is, perhaps, one of the most dangerous from the point of view of gonadal injury. With this in mind, intravenous pyelography was selected as the basis of a study to be approached from the following aspects: (1) the establishment of stricter criteria as indications for this procedure, (2) the determination of the gonadal dosage received during pyelography, and (3) a consideration of the practicality of providing physical protection to the gonadal areas.

The first part of our study consisted of a review of the records of 200 consecutive hospital and clinic patients who had undergone intravenous pyelography in the radiology department of the Albany Hospital from Oct. 20, 1955, to Feb. 2, 1956. There were several private outpatients examined during this period whom we have not included because their complete records were not available to us. We deliberately did not include current cases but instead went a year back into our records in order to avoid the tendency to "overread" films in those individuals who had certain signs or symptoms that we had come to regard as significant. We reviewed the hospital records in an attempt to obtain the following information: reason

From the Department of Radiology, the Albany Medical College and the Albany Hospital.

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for requesting the pyelogram; presence of symptoms suggesting disease of the urinary tract (hematuria, dysuria, frequency, and colicky pain), history of previous disease of the urinary tract; physical signs suggesting ureteral, renal, or bladder disease; abnormal findings on urinalysis; results of kidney function tests; and interpretation of the pyelogram. Our original hope had been to find some absolute correlation of one or more positive symptoms, signs, or laboratory tests with the finding of abnormality on the pyelogram. This was not an attempt to evaluate the accuracy of the latter as a diagnostic study. Unfortunately, we were unsuccessful in finding absolute correlation, although we did ascertain that the presence of certain historical, physical, or laboratory findings indicated the likelihood of an abnormal pyelogram.

Of 200 pyelograms, 55 were interpreted by the radiologist as demonstrating pathology. The history of characteristic colicky pain was the most accurate single finding indicating abnormality, almost invariably a calculus, in three out of five patients. Three of the six patients in whom the examiner palpated a possible renal mass were found to have enlarged kidneys. When gross or microscopic hematuria was present, pathology was demonstrated on two out of every five pyelograms. When urinalysis indicated the presence of white blood cells, one patient out of every four was found to have an abnormal pyelogram. When costovertebral-angle tenderness was present clinically, one out of every five patients had pathology demonstrated on the intravenous studies. Combination of symptoms, physical findings, and positive laboratory tests led to some increase in the accuracy of the predictions. If a person had costovertebral-angle tenderness and hematuria, he had one chance in two of having an abnormal pyelogram. If he had colicky pain and gross or microscopic hematuria, the chances were two out of three.

It became apparent as we analyzed the study that we could not accurately predict the presence of pathology by a simple analysis of signs, symptoms, and laboratory findings. Therefore, we found it necessary not only to include the above, but also to take into account certain recognized diseases which are often accompanied by a significantly high percentage of renal abnormality. Our list of indications is actually a modification of several lists that have appeared in the literature and in various textbooks.

Indications for Pyelography

This list of indications is as follows: 1. Typical history of renal or ureteral colic. This is a severe pain starting in either costovertebral region and radiating eventually anteriorly and often into the groin. 2. Mass in the kidney region. 3. Hematuria, gross or microscopic. In a woman, this must be on the basis of a catheterized specimen. 4. Carcinoma of the cervix (preliminary to treatment usually). In these patients, there is no need to worry about future genetic damage in view of the patient's age and the imminent surgical or radiation sterilization. 5. Hypertension. This is a somewhat misused indication. It is our impression that a large number of unnecessary pyelograms are being done when a plain film of the abdomen, studies with phentolamine (Regitine) methanesulfonate, and use of aforementioned criteria would often suffice. 6. Accidental or surgical trauma to the urinary tract. 7. History of renal or ureteral disease in the presence of recurrent symptoms. 8. Possible congenital neurogenic bladder. 9. Adrenal tumor. 10. Postoperative urinary tract procedure in the presence of recurrent symptoms.

Routine use of this list of indications is unfortunately unwieldy, but, in reviewing our cases, we find that about 75% of our pyelograms were clinically justified. On the basis of this list of indications, 51 of the 55 abnormal pyelograms were included. Of the four patients with abnormal studies not included, two were patients with asymptomatic renal calculi, one was a patient with an ectopic kidney which did not seem to be causing the patient's symptoms, and one was an individual with nonfunction of one kidney which our urologists felt was secondary to a recently passed ureteral calculus. We believe, therefore, that by adhering closely to these indications, we could eliminate one-fourth of our pyelograms while missing little of significance.

Measurement of Dose to Gonads

Any attempt to measure the quantity of radiation received by the gonadal tissues during intravenous pyelography is fraught with inaccuracies. It is well known that the output of diagnostic x-ray apparatus varies considerably due to many factors such as varying line voltages, tube-cathode temperatures, and exposure times. Nevertheless, since a review of recent literature revealed only a few reports of the radiation dose incidentally administered to the gonads during pyelography, we decided to measure this. The dose in the male was determined by placing a thimble chamber in contact with the scrotum. We believe that Stanford and Vance [1] were correct when they assumed that the value obtained represented the maximum dose to the reproductive organs. Although we have no studies to prove it, the air dose is thought to be about equivalent to the depth dose at 1 cm., which certainly would include the more superficial portion of the testis. The quality of the radiation that we used was "soft" (65-100 kvp range), but we feel that the beam was "hardened" by use of a 3-mm. Al filter and that the scatter was increased by the large volume of tissues through which the radiation was distributed. Our doses to the testes ranged from 0.1 r to 4 r. The doses in the lower range were thought to be due largely to the effects of scatter, while the doses in the range of 2 r to 4 r were higher, probably because the primary beam encompassed the scrotal region.

In the female it is more difficult to estimate the number of roentgens received by the germinal tis-

sues. Unless one can use the direct method in which a measuring device is placed in the vagina and, therefore, lies in close approximation to the ovaries, one must use depth-dose tables. We chose the latter method and placed the thimble chamber on the anterior abdominal wall over the pelvic region. We assumed, as have other workers, that the ovaries lie at a point midway in the pelvis. Our air-dose measurements ranged from 0.7 r to 4.1 r. Using the depth-dose tables for diagnostic x-ray apparatus compiled by Ritter, Warren, and Pendergrass [2] and making the necessary corrections for differences in equipment and filtration, we estimated the ovarian doses to lie in the range of 0.2 r to 0.5 r.

It was our experience that the testes practically always received a larger quantity of radiation than did the ovaries, presumably because of their more superficial location. When the primary beam is not well collimated or when the central ray is more caudad than usual, due to positioning, the male germinal tissues will receive considerably more radiation. Because of the large number of variable factors present, we do not consider our measurements to be entirely accurate. It might be better to state that during intravenous pyelography in adults, the ovaries appear to receive doses that are generally less than one roentgen, while the testes may, and often do, receive several roentgens.

Method of Decreasing Gonadal Radiation

The third portion of our project was a study of the possible methods of decreasing gonadal doses. For many years, workers have advocated employing various procedures and devices to decrease the amount of radiation to which the patient is exposed during routine x-ray examinations. Certain of these suggestions, such as the use of a filter of aluminum, usually from 1 to 3 mm. in thickness, and the use of cones or diaphragms to collimate the beam, have been widely employed. However, the proposal that the gonads of children or young adults be shielded during x-ray examinations, although suggested by many workers, has not been widely employed in the x-ray departments of our city or, to our knowledge, in the departments of other cities.

Protection of the germinal tissue of the male during pyelography is a simple matter, as the testes can be covered with a thin piece of lead or lead rubber without interference with the visualization of the lower ureter or bladder. It is obvious in the female that any attempt to protect the ovaries would result in obscuration of the pelvic portions of the ureters and of the bladder. We therefore decided to review our cases of ureteral pathology as diagnosed on intravenous pyelography to determine if there was any correlation between the demonstration of pathology and the time sequence of the x-rays after the injection of the contrast medium.

In the past five years, we have performed over 4,000 intravenous pyelograms in our department. Our routine calls for films exposed at 5, 10, and 15 minutes after injection of the opaque medium. These films are inspected "wet," and additional "delayed" exposures are made if it is felt by the examiner that valuable information will be thereby obtained. A review of the department cross-index for the past five years revealed 87 cases of ureteral abnormality or pathology detected on the intravenous pyelogram. We found that most of the ureteral pathology was demonstrated on "delayed" films which were made because of unilateral retarded excretion or because of unilateral hydronephrosis. A significant finding, however, was that in only 3 of the 87 cases could the pathology be demonstrated on the 5-or-10-minute films but not on the 15-minute or subsequent films. Interestingly, these three were all examples of double ureters. Two of them involved the abdominal portion of the ureter, so that they would have been visualized despite the covering of the pelvic portions of the ureters by a lead shield. The third was a case of double ureter on the right which was diagnosed by demonstration of the pelvic courses of both ureters on the 10-minute film only. In none of these three cases could it be said that the presence of the double ureter was the cause of the patient's symptoms. Therefore, in our series, in no instance was the 5-minute or 10-minute film vital to the diagnosis of significant lower ureteral disease. Because of this finding, we feel that during the "early" films we are justified in protecting the ovarian regions with a lead shield, the upper edge of which is at the level of the iliac crests. We realize that we will "hide" many normal ureters, but we feel that for the reasons stated the pathological ureter will fill on the 15-minute or delayed film.

Summary

A review of the records of 200 patients who had undergone intravenous pyelography revealed that about one out of every four pyelograms was unnecessary and could have been avoided if the clinicians had observed more carefully certain indications. During intravenous pyelography in adults, our studies indicate that the ovaries probably receive doses that are less than one roentgen, while the testes often receive several roentgens. The amount of radiation to the gonadal regions can be appreciably decreased without interfering with the diagnostic accuracy of the examination. A piece of lead or lead rubber is used to cover the testes in the male patient and the same is employed to cover the lower half of the abdomen in the female patient.

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METHODS IN EVALUATING ETHOHEPTAZINE AND ETHOHEPTAZINE COMBINED WITH ASPIRIN

Leo J. Cass, M.D., Willem S. Frederik, M.D., Ph.D.
and
Anthony F. Bartholomay, S.D., Brookline, Mass.

The efficiency of ethoheptazine as an analgesic was investigated in two series of observations. The first series, involving 71 patients with arthritis and other painful conditions, was set up to compare the effects of lactose as a placebo), aspirin, aspirin plus codeine, aspirin plus ethoheptazine, and ethoheptazine alone. The drugs were administered in capsules with certain precautions that prevented both the patient and those who appraised his responses from knowing which of the five kinds of capsules he was receiving. The results showed that aspirin and ethoheptazine were potent analgesics when given singly, and that when they were given together their combined effect was greater than that of either alone. Ethoheptazine 100 mg. alone was more efficient than aspirin 600 mg. alone. The second series, involving 35 patients, was set up to compare the effects of lactose (as placebo), aspirin plus ethoheptazine, and aspirin plus codeine. The results showed that the two mixtures were about equally good and that both were better than the placebo. Ethoheptazine in the dosage used caused less side-effects than did the placebo. This study illustrates two comparative statistical methods.

The general pharmacological properties and analgesic potency of ethoheptazine (Wy-401), 1-methyl-4-carbethoxy-4-phenylhexamethylenimine, in animals have been reported.[1] The clinical effectiveness and safety of this and other members of the hexamethylenimine series of analgesic compounds have been reported by Grossman and others and Golbey and others.[2] These studies indicate that ethoheptazine is an active analgesic which does not cause sedation, disorientation, constipation, suppression of cough reflex, or change in pupil size and that it does not have addiction liability.[3]

The primary objective of this study was to determine the relative clinical effectiveness of ethoheptazine and a combination of ethoheptazine and aspirin as analgesic agents in relation to certain known compounds of recognized value and also in relation to a placebo.

In order not only to test the clinical effect of the drugs but also to obtain a check on the methods used, two parallel techniques were employed. In one portion of the study, the double-blind technique was used and the results were subjected to statistical analysis. In the second portion, a single-blind technique was used and the data were subjected to sequential analysis. Sequential analysis is an a priori form of statistical analysis which treats the number of observations as a random variable and calls for the termination of the experiment just as soon as enough data are at hand to support a proposed hypothesis at an arbitrarily high level of statistical significance. This method has proved economical and useful in industry and in certain phases of wartime research.[4] This, however, is one of the few times that sequential analysis has been used in a study of this type. As indicated by the results of the second portion of this study and of previous studies by Bartholomay [5] and by Armitage,[6] such a method of analysis is proving to be a useful tool in clinical investigation. The number of observations required for validation of the hypothesis of effectiveness by the sequential probability ratio test (SPRT) is far less than the number usually chosen arbitrarily for such a study, but the degree of statistical significance that can be attached to the results would appear to be as high as one could require. It therefore constitutes a new and powerful tool for studies of this type.

From the University Health Services, Harvard University.

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Plan of Study

In the first or completely blind portion of the study, the clinical effectiveness of the analgesic compounds subjected to testing was determined by administering the medicaments to 100 hospitalized patients with chronic pain due to various causes.

The diagnoses of the patients included in the study were as follows for the 71 patients who completed the study: rheumatoid arthritis, 20; hypertrophic arthritis (spine, neck, and head-neck), 20; metastatic carcinoma, 8; neurological disorders with deformity, amyotrophic lateral sclerosis, and progressive muscular dystrophy, 5; phantom limb after amputation and other similar limb pain, 6; cardiovascular disease, cerebrovascular accident, and hypertension, 9; and nonunion of fracture, 3.

The diagnosis for 29 patients who did not complete the study were as follows: rheumatoid arthri-

tis, 11; hypertrophic arthritis, 9; cardiovascular disease, 6; nephritis, 1; amputation, 1; and gangrene of the foot, 1.

The patients ranged in age from 42 to 78 years. Two-thirds of the patients were males. Most were semiambulatory, in that they were allowed bathroom privileges and meals were taken in a dining room adjacent to the ward. In each case the patient suffered pain of sufficient severity to require analgesics, and most had previously received aspirin or codeine and aspirin routinely for relief.

The usual precautions for double-blind study techniques, as set forth in previous publications,[7] were observed. All patients received each of the test medicaments at random. The test period was seven days for each medicament. There was no rest period between medications. The random rotation of administration was considered adequate to compensate for any carry-over of analgesic action. The five compounds to be tested were prepared in capsule form, and all capsules were identical in appearance. Medicaments were delivered in five separate cartons, labeled A, B, C, D, and E, each containing 100 bottles of the same drug. Each of the 500 bottles had a different number. Delivery was made in this manner so that a preselected, randomized order of administration of the five compounds could be prepared for each patient. These "patient packages" of five bottles, to be given in a preselected order, were stored in a special closet to which only the ward nurses had access. The individual who was responsible for the randomization had no contact with the patients and had no knowledge of the compounds contained in the cartons, although he did know that five compounds, one of which was a placebo, were being tested. Naturally, the code was not revealed to any of us until after the data were analyzed and the medicaments were rated according to the clinical effectiveness of each.

The dosage used throughout the study was two capsules four times a day. The patients were questioned, in a standard manner, three times a day by a "disinterested" technician, and note was made of the degree of relief reported (no relief, very slight, moderate, almost complete, or complete) and the daily mean, side-effects (nausea or vomiting, vertigo, constipation, excitement, drowsiness, and shakiness), and any other pertinent information concerning other medicaments given, spontaneous remarks of patient, actual vomiting, cramps, or diarrhea, and type of pain.

The five drugs tested by the double-blind technique and the dosages given were as follows: (1) aspirin, 600 mg., (2) ethoheptazine hydrochloride, 100 mg. (equivalent to 87.8 mg. base), (3) codeine sulfate, 30 mg., plus aspirin, 600 mg., (4) ethoheptazine citrate, 100 mg., plus aspirin, 600 mg. (Zactirin), and (5) placebo (lactose). The amounts indicated represent the amounts contained in each dose (two capsules).

In the single-blind portion of the study, three medicaments, labeled no. 1, no. 2, and no. 3, were used in the test. The three were supplied in capsules which were identical in appearance. In this case, it was necessary to supply one of the investigators with the code so that the drugs could be given in pairs, in order to apply the double dichotomy form of the SPRT. Actually, however, the medicament being administered was not known by observer, statistician, or patient. This was accomplished by tearing off the label. It was known that three agents were involved: a placebo, codeine plus aspirin, and ethoheptazine plus aspirin.

Patients subjected to this portion of the study included ambulatory custodial patients with transient pain, such as that caused by headache, arthritis, bursitis, and other conditions commonly seen in outpatient practice. All patients were males between the ages of 58 and 84 years. The same medicament was administered to a given patient three times daily or as needed. The dose in each case was two capsules, and the amounts of the drugs contained in each dose were the same as used in the double-blind study with five unknown agents. The response after each administration was graded after questioning by an observing nurse. The report chart for this portion of the study was similar to that for the other, and the degree of pain relief was graded in the same manner.

Evaluation of Results

The first and second portions of the study were treated independently. Therefore, the results of both parts are reported separately in order to facilitate a comparison of the two approaches.

In the double-blind study, involving five unknowns, the drug therapy in all 100 patients was started on a given date and the medicament was changed every seven days until the study was completed. Seventy-one patients completed the study. The accumulated data were then subjected to analysis, and the medicaments were graded according to the clinical effectiveness of each. The total number of observations, therefore, was $71 \times 3 \times 7 \times 5$, or approximately 7,500. If a patient refused medication even once he was dropped from the study. Refusals or absence from the wards for various reasons accounted for 22 of those patients who did not finish the study. In addition, four patients were transferred, one had persistent nausea, and one died of gangrene associated with severe arteriosclerotic vascular disease and hemiplegia.

The first step in the statistical analysis was calculation of the average effectiveness of each of the five drugs under study. This average effectiveness was calculated by adding the 21 numerical values of the observations made during one week of treat-

ment in each patient. The 71 individual sums were then added and divided by the total number ($3 \times 7 \times 71$) of all observations of this drug. The patient's preference or rating for each of the five coded drugs was computed. Each drug was rated 1, 2, 3, 4, or 5, 1 being the least and 5 the most effective. Table 1 shows the five coded drugs ranked according to average effectiveness and the number of times each rating by a patient was recorded for each of the five drugs.

Drug A received the lowest total score by 58 patients, which would indicate that it was the least effective agent; only 1 patient found this drug the most effective. Drug E never received the lowest total score, and B and D only rarely were rated as the least effective.

In order to interpret the data in this table, we calculated the weighted average for each drug. This was done by multiplying the number of patients by their rating number for a specific drug. The five products were then added and the sum was divided by the number of patients. The weighted average of drug A is, therefore, 1.27 ($58 \times 1 + 10 \times 2 + 1 \times 3 + 1 \times 4 + 1 \times 5$, divided by 71).

The weighted averages for the five coded drugs are, in order of rank, for A, 1.27; C, 2.18; B, 3.65; E, 3.90; and D, 3.99. The ranking of the weighted averages of the various drugs corresponds closely to the average effectiveness, as shown in table 1, with the exception of drugs D and E, which are reversed in order.

Notwithstanding the fact that two different approaches of evaluating the test results provided practically identical information, it still must be proved that the averages are actually significantly different. Various t-tests were performed with the data obtained from the different medicaments in pairs. (The t-test is a widely used, short statistical

TABLE 1.—*Average Effectiveness of Each Drug with Patients' Rating*

Rank*	Code	Effectiveness Av.	Patient's Rating 1	2	3	4	5
1	A	0.265	58	10	1	1	1
2	C	1.469	10	42	15	4	0
3	B	2.592	2	6	23	23	17
4	D	2.521	1	6	15	22	27
5	E	2.588	0	7	17	23	24

* Ranging from 1 (least effective) to 5 (most effective) in order of effectiveness.

procedure in which the likelihood that two sets of data are significantly different can be calculated—in other words, that any pair of medicaments are or are not significantly different in effect. When the t-values are given, the degree of accuracy of the conclusions can be checked by the reader.) It was not possible to find a significant difference between drugs D and E, and we must, therefore, conclude that these are identical in effectiveness as pain relievers. Drug A was significantly less effective than any of the other four drugs. Table 2 presents some of the important t-values resulting from the comparison of pairs of drugs.

At this stage of the investigation the code was given to us. Drug A was placebo; B was ethoheptazine; C was aspirin; D was ethoheptazine plus aspirin; and E was codeine plus aspirin.

TABLE 2.—*Results of Statistical Procedures in Comparison of Drugs*

Drug Pairs	t-Value*	p
A-B	16.77	<0.01
A-C	8.06	<0.01
B-C	11.17	<0.01
B-D	2.00	=0.05
B-E	2.55	<0.02
C-D	11.09	<0.01
C-E	13.71	<0.01
D-E	0.55	>0.50

* t-values for 20 degrees of freedom. When p is 0.05, t = 2.09; when p is 0.02, t = 2.38; and when p is 0.01, t = 2.67.

From the previously given t-values, the following conclusions can therefore be made: 1. Ethoheptazine in a dose of 100 mg. plus aspirin in a dose of 600 mg. is as active a pain reliever as codeine in a dose of 30 mg. plus 600 mg. of aspirin (when D and E are compared, t=0.55). 2. Aspirin alone, 600 mg., has a definite pain-relieving action as compared with a placebo (when A is compared with E, t=8.06). 3. Ethoheptazine, 100 mg., is more efficient than 600 mg. of aspirin alone (when B is compared with C, t=11.17). 4. Addition of 600 mg. of aspirin to ethoheptazine provides a significant increase in efficiency (when B is compared with D, t=2.00). 5. Addition of codeine, 30 mg., to aspirin, 600 mg., causes a significant improvement in pain relief (when C is compared with E, t=13.71). 6. Ethoheptazine, 100 mg., has a highly significant analgesic effect as compared with a placebo (when A is compared with B, t=16.77). 7. Codeine, 30 mg., plus aspirin, 600 mg., is significantly more effective than ethoheptazine, 100 mg. (when B is compared with E, t=2.55). 8. Ethoheptazine, 100 mg., plus aspirin, 600 mg., is more effective than aspirin alone (when C is compared with D, t=11.09).

In the single-blind portion of the study, the estimate of effectiveness of the medication for the entire day was made from the average of the three response indexes. Generally, an average of 2.67, which represents approximately 70 to 80% effectiveness, was regarded as a "success," an average less than this, a "failure." There were exceptions to this rule, e. g., a record of 1, 2, and 4 would be regarded as a success. This transformation amounted to a meaningful way of changing semiquantitative data into all-or-none form, a form which is required by the structure of the SPRT.

The binomial form of SPRT * was used to test the hypothesis that a medicament, to be effective, must show less than 20% failure. To test such a

hypothesis for a given medicament, the number of failures (d_m) must be plotted on a "sequential grid sheet"* against the total number of observations (m), adding points as the observations accumulate. The "grid" is composed of pairs of "acceptance" and "rejection" lines, each pair corresponding to a

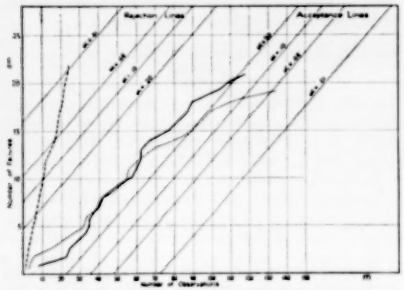

Fig. 1.—Sequential probability ratio test of hypothesis that a given medication is more than 80% effective. Drug no. 1 is shown by straight line, no. 2 by broken line, and no. 3 by dotted line.

given level of statistical significance. Generally, the lowest acceptance level is 5%, indicating that there are 5 chances in 100 of error in the decision either to accept or to reject the proposed hypothesis. The points (m and d_m) are joined to form a polygonal sequential curve. The first time that this curve crosses an acceptance line, the hypothesis is accepted at the corresponding statistical level and the

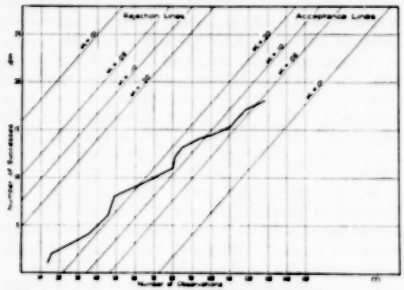

Fig. 2.—Sequential probability ratio test of hypothesis that drug no. 2 (placebo) is less than 20% effective.

experiment is terminated; if it first crosses a rejection line, the hypothesis is rejected at the corresponding level and the experiment is terminated.

After 130 observations on 35 patients, the hypothesis that no. 3 was effective in more than 80% of the cases was accepted at the 5% level (fig. 1). After only 16 observations, this same hypothesis applied to no. 2 was rejected also at the 5% level. In the case of no. 1, there were not enough successes in 130 observations either to accept or to reject this hypothesis—further observations would have to be made. Inspection of figure 1 shows that after 130 observations had been made, the trend of the sequential curve for no. 1 was most definitely in the direction of acceptance at a higher level.

The testing was continued with no. 2 to see if a hypothesis could be validated to the effect that no. 2 should be effective in less than 20% of all cases. As figure 2 shows, this hypothesis was accepted at the 5% level after 130 cases.

These results seemed to indicate that no. 3 was either ethoheptazine plus aspirin or codeine plus aspirin and that no. 2 was a placebo. A "double dichotomy" [4] type of sequential test was applied separately to see if the difference between no. 1 and no. 3 was detectable. After 30 observations this test was abandoned because there seemed to be no

Table 3.—*Side-effects Recorded During Study of Drug Administration in Seventy-one Patients*

Side-effects*	Drug Used†				
	Placebo (A)	Ethoheptazine (B)	Aspirin (C)	Ethoheptazine and Aspirin (D)	Codeine and Aspirin (E)
Nausea or vomiting, no.	5	2	3	1	1
Vertigo, no.	0	1	1	2	1
Constipation, no.	1	0	1	1	1
Excitement, no.	5	3	2	2	2
Drowsiness, no.	2	1	0	4	1
Shakiness, no.	3	3	1	2	1
Total	16	10	8	12	7

* Given in number of patients in whom each was recorded.
† Letter in parentheses refers to code used in study.

evidence whatever of a perceptible difference between the two. This gave further presumptive evidence that in the long run the course of no. 1 should approximate that of no. 3.

At the conclusion of our sequential testing procedure, the identity of the code numbers was made known. As predicted, no. 2 was the placebo, no. 1, ethoheptazine plus aspirin, and no. 3, codeine plus aspirin.

In the group of 100 patients receiving the five coded drugs, an attempt was made to gather data concerning the side-effects observed or of which reports were volunteered. The number of patients experiencing certain side-effects during the treatment period is presented in table 3. This represents some repetition of patients. Actually, out of 71 patients completing the study, 18 experienced side-effects, 13 to one drug and 5 to more than 1 drug. Thus, 18 patients experienced one or more side-effects to one or more drugs for a total of 25 instances of side-effects in 5×71 patient treatment courses, which were distributed as follows: A, 8; B, 5; C, 4; D, 6; and E, 2.

The number of side-effects experienced after any given medication and the number of specific side-effects occurring after any given medication were too small to warrant the drawing of conclusions. Also, as has been pointed out by others, liability of analgesic agents to give side-effects is more properly determined in healthy adults.

Comment

Comparison of the results of the two techniques reveals a high degree of agreement. Using the t-test, five unknowns were tested and the relative clinical effectiveness of each was determined. By sequential analysis, alternates only were measured against one another. An advantage in this method lies in its value in determining whether a given medicament has a measurable clinical effect in comparison with a placebo or a known drug. If the clinical differences are slight, a large number of observations might be required before the zone of significance is entered, although this number could be lower than that required in a complete variance analysis. This particular study proved fortunate for comparative purposes, since the clinical differences between the medicaments were sufficiently marked to permit a clear-cut decision as to the relative effectiveness of each drug.

Conclusions

With use of both a completely blind study technique (71 patients) and a single-blind method (35 patients) and employing sequential analysis, the following conclusions became evident relating to the effectiveness of ethoheptazine therapy.

Ethoheptazine, in doses of 100 mg., was found to be more active than aspirin as an analgesic. However, the same dose of ethoheptazine, given in combination with 600 mg. of aspirin, was found to have an analgesic action of the same level of effectiveness as codeine in doses of 30 mg. in combination with 600 mg. of aspirin. At the dosage levels used, there were no significant side-effects.

A cross comparison reveals a high degree of accuracy in the completely blind method with confirmation by sequential analysis in this particular study. Of general scientific interest in this work is the role which has been demonstrated for sequential analysis in drug-testing experiments.

1101 Beacon St. (Dr. Cass).

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THE PREDIABETIC STATE AND LARGE BABIES.—Probably all who have cared for many diabetic patients have had occasion to observe some of the characteristics of diabetes in individuals who lacked any detectable evidences of disturbed carbohydrate metabolism. Even the response to the glucose tolerance test has been normal. But, after some years have elapsed hyperglycemia and glycosuria appear. A common indication of a prediabetic state is seen in women who give birth to large babies. The prediction that the mother of an infant weighing more than 10 pounds at birth will ultimately develop clinical diabetes is more likely than not to be fulfilled. This result is especially likely if the mother has diabetic relatives. —G. G. Duncan, The Modern Aspects of the Diabetic Problem, *Bulletin of the New York Academy of Medicine*, February, 1958.

PAM (PYRIDINE-2-ALDOXIME METHIODIDE) THERAPY FOR ALKYLPHOSPHATE POISONING

Tatusji Namba, M.D., Ph.D.
and
Kiyoshi Hiraki, M.D., Ph.D., Okayama, Japan

The prompt antidotal effect of PAM (pyridine-2-aldoxime methiodide) in alkylphosphate poisoning was demonstrated in five cases here reported. The patients were all farm workers who had been spraying fields with parathion. Cholinesterase determinations in both serum and erythrocytes were carried out and clearly showed the inhibitory effect of the parathion upon the enzyme. Intravenous administration of PAM relieved some of the symptoms instantly, and cholinesterase determinations demonstrated the reactivation of the enzyme. PAM was effective after either oral or parenteral administration and could be given in adequate doses without disagreeable side-effects. It also relieved certain symptoms, such as muscular fasciculation, that are not relieved by atropine.

Of the many alkylphosphate compounds synthesized in the past 20 years, some have come to be used practically as remedies (isoflurophate [DFP]) or as insecticides (tetraethylpyrophosphate [TEPP], parathion), especially after World War II.[1] In Japan, parathion has been widely used as an agricultural insecticide, mainly for rice cultivation, since 1952, and its use has been encouraged by the Ministry of Agriculture and Forestry in order to increase the rice crop. It is the consensus of opinion that the use of parathion as an insecticide was in a large measure responsible for the bumper crop of rice in 1955 in Japan. Useful as it is, parathion also has its shortcoming, namely, parathion poisoning. The estimated number of victims during the past five years is said to be over 6,000. Consequently, many studies have been made on poisoning by alkylphosphate compounds, and, on the basis of numerous clinical observations,[2] we established a standard atropine treatment[3] by which many victims of parathion poisoning have been saved in Japan. However, it is to be regretted that atropine is not the specific medicament.

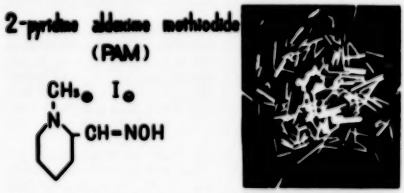

Fig. 1.—Structural formula and crystal of PAM (pyridine-2-aldoxime methiodide).

Recently, I. B. Wilson and his colleagues of Columbia University introduced PAM (pyridine-2-aldoxime methiodide) as a specific reactivator of alkylphosphate-inhibited acetylcholinesterase. The inhibition of this enzyme had been shown by Nachmansohn to be the cause of the toxic effects of alkylphosphates.[4] PAM successfully reactivated the inhibited acetylcholinesterase in vitro,[5] and hundreds of mice injected with lethal doses of alkylphosphates were spared their lives by PAM injection.[6] But in vivo, the mechanism of PAM has not yet been pursued in full detail, especially so with regard to its clinical effects.[7] PAM is a yellow rhombic crystal with a melting point of 219 C (decomposed). It is 5% soluble in water and practically insoluble in alcohol. The structural formula of PAM is shown in figure 1. PAM itself does not hydrolyze acetylcholine in vitro. The LD_{50} (milligrams per kilogram of body weight) of PAM on mice was estimated as 136[6] and 209[7] (187-233) in the case of intraperitoneal injection, and 140 (125-157)[7] by subcutaneous injection. In the present study, 5% PAM solution in water was used. The present paper is intended to report in vivo experiments with laboratory rabbits and the therapeutic effects of PAM on human patients suffering from acute parathion poisoning.

Blood cholinesterase activity was assayed manometrically with Tamai's modification[8] of Ammon's method[10] at 38 C in a medium containing 0.124 *M* sodium chloride, 0.025 *M* sodium bicarbonate, 0.0025 *M* potassium chloride, 0.0018 *M* calcium chloride, and acetylcholine as substrate (0.025 *M* for human serum cholinesterase and 0.0025 *M* for animal serum cholinesterase). The estimation of cholinesterase activity was based on carbon dioxide volume produced during 30 minutes after the addition of substrate. The determination of mucoprotein and protein sulfhydryl (SH) radical activity was performed polarographically.

From the Department of Internal Medicine, Okayama University Medical School.

White male rabbits, each weighing about 2 kg., were used. PAM itself had no influence on the general appearance and blood cholinesterase activity of rabbits. Subcutaneous injection of 10 mg. per kilogram of body weight of parathion emulsion (approximately LD_{50}) resulted in an inhibition of blood cholinesterase and produced symptoms of poisoning such as muscular fasciculation, salivation, and noisy respiration. Intravenous administration of PAM in a rabbit previously injected with parathion emulsion resulted in a striking reactivation of blood cholinesterase and the disappearance of symptoms in a short period of time (fig. 2, *upper left*). Twenty-four hours after the parathion injection, however, this rabbit died due to the reinhibition of cholinesterase, proving the effect of PAM to be only transient.

Repeated injections of relatively large doses of PAM maintained the blood cholinesterase activity after it had been restored, and no symptoms could be observed (fig. 2, *lower left*). The same method of PAM administration proved to be capable of prolonging the life of a rabbit that had received even as high a dose as 50 mg. per kilogram of body weight of parathion by injection. In this animal, the first PAM injection was the most effective in reactivating cholinesterase, but later injections gradually lost their effectiveness (fig. 2, *upper right*). In these experiments, PAM was injected while cholinesterase activity was being inhibited by parathion and the effect of PAM was transient; but the cholinesterase reinhibition was slight when PAM was given in the course of natural cholinesterase recovery (fig. 2, *lower right*). PAM was equally effective when given by subcutaneous injection (fig. 3, *upper left*) and orally (fig. 3, *upper right*). Oral administration of PAM could likewise protect against the cholinesterase-inhibiting action of parathion (fig. 3, *lower left* and *right*).

Parathion poisoning is divided into four types,[3] namely, serious, moderate, slight, and latent. This classification is now being used widely in Japan. The five cases reported here were all serious.

Report of Cases

Case 1.—A 17-year-old boy sprayed a rice field with a parathion solution. The next evening he became ill. After receiving by injection 20 ampuls of atropine, each containing 0.5 mg., the patient was brought to our clinic three hours after the onset of symptoms (Sept. 2, 1956). He then was in the convalescent stage. An intravenous injection of 0.1 Gm. of PAM produced neither changes of symptoms nor toxic effect, but a transient, slight recovery of red blood cell cholinesterase (fig. 4, *upper left*). This boy improved six hours after the onset of poisoning.

Case 2.—A 24-year-old farmer sprayed a rice field with a parathion solution. In the afternoon of the following day (Sept. 2, 1956) he fell ill, with nausea, vomiting, abdominal cramps, diarrhea, profuse sweating, salivation, involuntary micturition, muscular fasciculation, and coma. He was given 10 intravenous injections of 0.1 Gm. of PAM each during a period of three and one-half hours. By the time of the last PAM injection, all the symptoms had disappeared and no toxic effect of PAM was discernible. In this case, the changes of blood cholinesterase activity were impressive in that the red blood cell cholinesterase was reactivated by degrees and rose above normal. On the other hand, serum cholinesterase activity increased only slightly, but it required only one-half the time for this activity to return to normal compared with that of untreated cases (fig. 4, *lower left*).

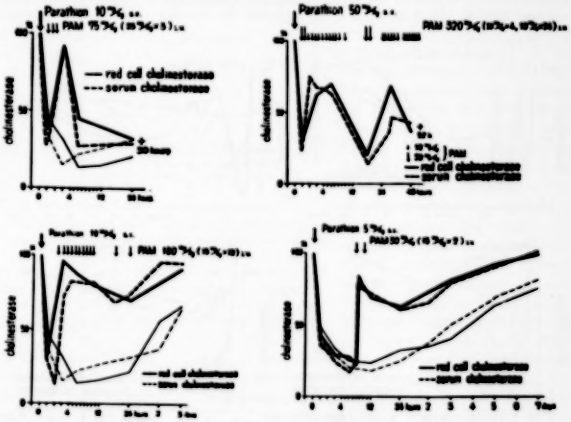

Fig. 2.—Blood cholinesterase activity in four rabbits injected with parathion then treated with PAM (heavy lines) compared with untreated rabbits (light lines). *Upper left*, transitory recovery. *Lower left*, continuous reactivation by repeated intravenous injections of PAM. *Upper right*, prolonged life and recovery of cholinesterase in rabbit injected subcutaneously with 50 mg. per kilogram of body weight of parathion. *Lower right*, slight reinhibition of activity during natural cholinesterase recovery.

Case 3.—This 24-year-old farmer had been engaged in spraying a rice field with a parathion solution. On the third day he fell ill and was admitted to our clinic (Sept. 3, 1956). He then complained of dizziness, nausea, vomiting, headache, salivation, profuse sweating, and slight muscular fasciculation. At once 0.5 Gm. of PAM was injected intravenously and no toxic sign appeared; therefore, another injection of 0.4 Gm. of PAM was made 10 minutes later. Immediately after the second injection, all the patient's complaints disappeared. Complete recovery of red blood cell cholinesterase took place 40 minutes after the PAM

injection, and serum cholinesterase activity was slightly increased and returned to normal in 15 days (fig. 4, *upper right*).

Case 4.—A 37-year-old farmer visited our clinic Sept. 10, 1956, on the eighth day after the onset of acute parathion poisoning. He was complaining of only slight headache and there were no positive physical findings. Blood cholinesterase activity was on the way to recovery. At the patient's request, a rapid intravenous injection of 1 Gm. of PAM was given. He felt discomfort for less than one minute and showed no toxic symptoms. The blood cholinesterase value revealed little change (fig. 4, *lower right*).

Case 5.—A farmer, aged 28, was admitted to this clinic Sept. 6, 1956. This case is supposed to be the first of parathion poisoning ideally treated with PAM and is, therefore, presented in detail. This man was engaged in spraying a rice field with 0.1% parathion solution. At 1:30 p. m. on the third day of work, he suffered from dizziness, profuse sweating, salivation, and tightness of the chest, but continued to work until 3 p. m. when nausea and vomiting began. Shortly thereafter he went home and thoroughly washed himself. At 4 p. m. he was attacked by severe

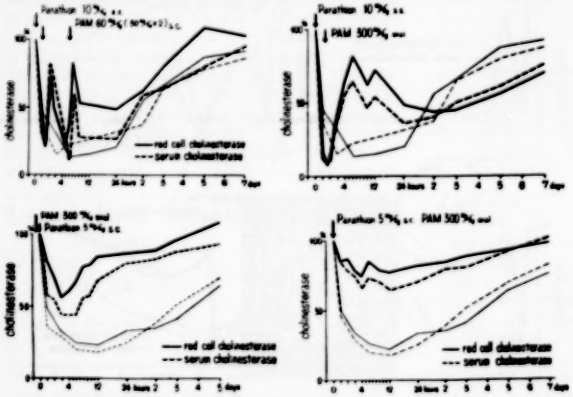

Fig. 3.—Blood cholinesterase activity in four rabbits injected with parathion then treated with PAM (heavy lines) compared with untreated rabbits (light lines). *Upper left*, transitory reactivation after single subcutaneous injection of PAM. *Upper right*, slower reactivation and reinhibition after oral dose of PAM. *Lower left*, slight inhibition after oral dose of PAM 30 minutes before subcutaneous injection of parathion. *Lower right*, slight and slow inhibition after oral dose of PAM administered simultaneously with subcutaneous injection of parathion.

dizziness, slurred speech, blurred vision, and coma. After the injection of three ampuls of atropine, he was brought to our clinic at 6:30 p. m.

Physical examination revealed a well-developed male, seriously ill and unresponsive. His respiration was slow and seemed difficult. The pulse rate was 130 per minute and blood pressure 170/111 mm. Hg. The body temperature was 37.5 C (99 F). Muscular fasciculation was very marked and generalized. He was no longer sweating but had excessive salivation. The pupils were pinpoint in size, reacting scarcely to light. The heart was slightly enlarged to percussion, with the heart sounds powerful and good. The lungs and abdomen were normal. Tendon reflexes of the extremities were absent. Cholinesterase activity of red blood cells was 28.9 ml. carbon dioxide volume, approximately 13% of normal, and that of serum was 4.9 ml. carbon dioxide volume, only 0.6% of normal. Serum mucoprotein was 38.8% and serum protein SH radical activity was 47.5% of normal. The leukocyte count was 19,900 per cubic millimeter, with 87% polymorphonuclear cells, 10% lymphocytes, and 3% monocytes. Eosinophils were absent. The hemoglobin value was 12.6 Gm. per 100 ml., with 5,170,000 erythrocytes per cubic millimeter. Urinalysis showed 1+ sugar, and ± urobilinogen with *p*-nitrophenol 133.8 mcg. per 100 ml. The blood sugar level was 149 mg. per 100 ml. Cephalin cholesterol flocculation, Takata-Ara, icterus index, and other tests on serum were normal. An electrocardiogram showed right bundle-branch block, probably having some connection with the poisoning.

At 6:37 p. m., seven minutes after admission, the patient was given 1 Gm. of PAM intravenously. The muscular fasciculations diminished instantly except in certain parts of the chest and legs. He was awake and responsive. At 6:41 p. m. blood pressure was 158/80 mm. Hg. Respiration quieted down. At 6:58 p. m., 21 minutes after PAM injection, the muscular fasciculation disappeared completely and no symptoms could then be found. The course of the blood cholinesterase activity is given in figure 5, *left*. This activity returned to normal within 10 minutes after the PAM injection, while the serum cholinesterase was reactivated only transiently, but returned to normal earlier than that of untreated patients. The courses of serum mucoprotein and serum protein SH radical activity are given in figure 5, *right*. Both show a course similar to that of serum cholinesterase. In other cases, serum mucoprotein and serum protein SH radical activity are also similar to that of serum cholinesterase.

Comment

The administration of PAM promptly relieved the symptoms of parathion poisoning. The effect observed was more remarkable in the clinical experiments than in the animal experiments. In case 1, the clinical improvement was scarcely noticeable, due probably to the small dose of PAM. In case 2, the effect was somewhat equivocal, but in cases 3 and 5, where a sufficient quantity of PAM had been administered in a single dose, dramatic effects were observed at the time of the injection; recovery of a clear consciousness, disappearance of muscular fasciculations, and improvement of respiratory function. In all of these cases, the dose of atropine was not large enough to affect the symptoms, except in case 1, in which PAM had little effect. The administration of atropine, which is considered to be an effective medicament for alkylphosphate poisoning, can relieve only a portion of the symptoms and does not affect others, such as muscular fasciculation. Besides, it has shortcomings in that it requires a large dose to be effective, with attendant unpleasant side-effects. With the administration of PAM, however, all the symptoms were relieved and there arose no unpleasant side-

effects. From this fact it may be said that PAM is the corrective and specific therapy for alkylphosphate poisoning.

Cholinesterase activity of red blood cells was instantly and completely restored, but the return of this activity in the serum was transient. Ten minutes after PAM injection, cholinesterase activity of red blood cells recovered to normal, as observed in case 5. Such a phenomenon could not be expected

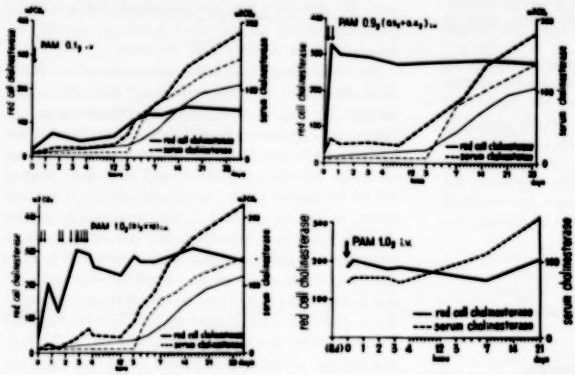

Fig. 4.—Blood cholinesterase activity in four patients with serious type of parathion poisoning treated with PAM (heavy lines) compared with untreated patients (light lines). *Upper left*, transient, slight recovery after intravenous injection of 0.1 Gm. of PAM (case 1). *Lower left*, recovery to normal after 10 intravenous injections of 0.1 Gm. of PAM in three and one-half hours (case 2). *Upper right*, instantaneous recovery after total of 0.9 Gm. of PAM given in two doses (case 3). *Lower right*, little change after 1 Gm. of PAM on eighth day after onset of poisoning (case 4).

with previous forms of therapy. The activity then decreased to some extent but remained within the normal limit in the human experiments. This finding is quite surprising, since without PAM administration the recovery of cholinesterase activity generally takes quite long (a month or more in serious cases), and it is not in any way affected by atropine treatment. The recovery of serum cholinesterase activity, however, was slighter and transient, but even the serum cholinesterase regained normal activity in about half the time as in untreated cases.

There are two types of cholinesterase, true or acetylcholinesterase and nonspecific pseudocholinesterase. In humans, the former is contained in the nervous tissue and red blood cells and is considered to play a role in neurohumoral transmission. The latter is contained in serum and is considered to have essentially no function in neurohumoral transmission but is related closely to liver function. In the rabbit, the serum cholinesterase is the same as acetylcholinesterase. Thus this fact may make it comprehensible why the values of both serum and red blood cell cholinesterase behave alike in the rabbit while they do not in humans and why, in humans, all the symptoms disappear without restoration of serum cholinesterase activity.

From these results, it is obvious that the main effect produced by the administration of PAM is the restoration of the activity of acetylcholinesterase and the effect on pseudocholinesterase is but secondary. As the cholinesterase of the nervous tissue is of the true type, PAM is remarkably effective in the treatment of alkylphosphate poisoning. Kewitz and Wilson [8] rightly assumed that PAM probably reactivates only acetylcholinesterase in vivo, basing their assumption on in vitro experiments in which it has been found that PAM is a much poorer reactivator of human serum cholinesterase.

At present the diagnosis of alkylphosphate poisoning is based mainly on a decreased serum cholinesterase (pseudocholinesterase) value and on physical examination. It has been generally accepted that the degree of the damage in vivo caused by alkylphosphate poisoning may be estimated more exactly by measuring the acetylcholinesterase. We would venture to recommend rather the measuring of serum

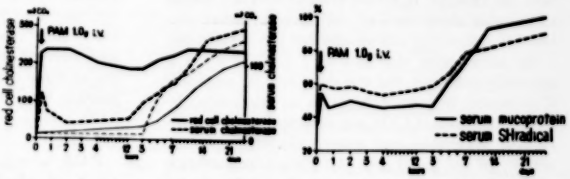

Fig. 5.—*Left*, instant and complete recovery of red blood cell cholinesterase activity and transient recovery of serum cholinesterase after single intravenous injection of 1 Gm. of PAM in patient with serious type of parathion poisoning (case 5, heavy lines) compared with untreated patient (light lines). *Right*, serum mucoprotein and serum protein SH radical activity show course similar to that of serum cholinesterase (case 5).

cholinesterase activity in making qualitative and quantitative diagnosis of alkylphosphate poisoning, because of the complexity of the determination of the activity of red blood cell cholin-

esterase and because of a relatively long time required in becoming proficient in the operation. Mydriasis, the most standard symptom of the diagnosis, has almost lost its significance in our clinic, as atropine is widely used in the treatment and nearly all the patients are admitted to our clinic after premedication with atropine. In the future, when PAM treatment attains universal recognition, it might be possible to diagnose the poisoning after administration of PAM, basing it not on the cholinesterase activity of red blood cells but on that of serum.

The behavior of serum mucoprotein varies in direct proportion to the activity of cholinesterase and the behavior of active protein SH radical of serum nearly coincides with that of serum mucoprotein. Changes other than cholinesterase activity in parathion poisoning have been recently observed by us with mucoprotein and active protein SH radical in serum, the findings of which are arousing a keen interest in Japan.[11] With PAM administration, the changes in serum mucoprotein are similar to those of cholinesterase, and those of active protein SH radical are also similar but less remarkable.

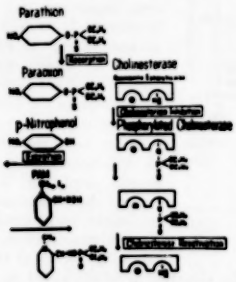

Fig. 6.—Schematic diagram of inhibition of cholinesterase activity by parathion and its reactivation by PAM.

An intravenous injection of 1 Gm. of PAM is generally sufficient, but the dose may be increased if necessary. In cases 2, 3, and 5, an intravenous injection of 1 Gm. of PAM was sufficient to relieve the clinical symptoms and restore the cholinesterase activity of red blood cells. After the administration of PAM, a transient decrease of red blood cell cholinesterase activity is apt to occur, and so in serious cases there may be a possibility of recurrence of the symptoms together with the reinhibition of cholinesterase. But from our experience we find that if the patient survives for as long as 12 to 24 hours after the onset of symptoms, he generally recovers spontaneously. From these facts, a 1-Gm. dose may be sufficient and, if needed, 1 or 2 Gm. more of PAM may be given. Now we are considering giving larger doses of PAM in order to treat parathion poisoning more effectively. We believe that this is especially necessary with cases where larger amounts of parathion are taken, as in suicide cases. Because of the time element involved in the treatment of parathion poisoning, PAM was administered intravenously, but the subcutaneous route may be employed as well. Oral administration may be effective but not practical, for parathion poisoning, even in its mild form, is usually accompanied by nausea and vomiting.

No side-effect has been encountered in PAM administration. The side-effect of any new drug should be taken into serious consideration. In laboratory experiments with mice, the intravenous LD_{50} of PAM was found to be 140 mg. per kilogram of body weight (125-156), and this dose turned out to be sufficient in actual application. Some patients, as in cases 1 and 2, who received a smaller dose of PAM had vomiting, but it seemed to be a symptom caused by parathion poisoning rather than the drug itself as no such side-effect was found in the patients in cases 3 and 5, who were given larger doses of PAM. The patient in case 4, who received a rather rapid intravenous injection of PAM, complained of a slight discomfort which lasted only one minute. Abnormalities of the blood picture or of liver function were not observed. No pains or local changes of vein and skin at the site of the injection appeared. These facts seem to indicate that there are no serious side-effects of the conventional administration of PAM now in use, not even in large doses.

PAM had no influence on the cholinesterase activity of normal blood. After the administration of PAM, the blood cholinesterase activity in normal rabbits remained within its normal range, and this was also true in man (case 4). Wirth[12] and Jensen[13] have reported that most of the phosphoric acid derived from parathion was excreted within one to three days and then only in a small amount. Judging from these facts, it might be assumed that PAM acts only with the phosphorylated parathion (fig. 6).

PAM is expected to be used as a preventive agent of alkylphosphate poisoning. As already mentioned, PAM exhibits no effect when intravenously administered in small doses for prophylactic purposes. This is probably due to the prompt excretion or inactivation of PAM. On the other hand, PAM administered orally may be assumed to be a preventive agent against the decreasing cholinesterase activity in rabbits. In man it is expected to be more effective than in the rabbit, as we have

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195

seen in its therapeutic uses. Hitherto, alkylphosphate poisoning has been treated mainly by atropine, but now atropine is replaced by PAM. With the advent of PAM as a remedial agent of the metabolic defect produced by the alkylphosphate and also the nerve gas poisonings, a rapid progress of the study on enzyme mechanism might be expected. We hope that this study will contribute somehow to the progress in the treatment of alkylphosphate poisoning and to the welfare of mankind.

Summary

With administration of PAM (pyridine-2-aldoxime methiodide) as a specific reactivator of alkylphosphate-inhibited acetylcholinesterase, a prompt and complete relief of symptoms of this poisoning can be realized. Cholinesterase activity of red blood cells is restored instantly and completely recovers; that of the serum recovers only transiently. Serum mucoprotein varies in direct proportion to serum cholinesterase, and active protein sulfhydryal (SH) radical of serum varies nearly the same. Generally, an intravenous injection of 1 Gm. of PAM is sufficient, but the dose may be increased when necessary. No serious side-effect has been encountered. PAM exerts no influence on the cholinesterase activity of normal blood. PAM is expected to play an important role as a preventive agent of alkylphosphate poisoning.

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LYMPHATIC LEUKEMIA FOLLOWING GAMMA RADIATION.—One of a group of 56 Yorkshire-Hampshire hogs died on the 196th day of an experiment during which all received, until death, 50 r daily of gamma radiation from Co-60 given at a rate of about 30 r per hour. . . . The leukemic hog was the 36th of the group to die. All others died within a year, of a chronic irradiation sickness. No other leukemia was observed. This hog had previously received 425 r of gamma radiation given continuously at about 1.5 r per hour and had been allowed a recuperation period of 3 months before the subsequent irradiation program was initiated. The total accumulated dose was 10,225 r measured in air. The hog weighed 140 lb. when the experiment was initiated, 320 lb. when the chronic daily exposures began, 540 lb. 1 week before death, and 510 lb. at the time of death. Two weeks before death, lethargy and a retrogression of general condition was observed, and a short walk usually produced exhaustion. No glandular enlargements were seen, although a splenic rigidity and enlargement could be palpated through the abdominal wall during the last week of life. . . . The most notable changes seen at necropsy were: the inflamed and pustular tonsilar area, the huge spleen (11 × larger than others of the group; 7 × on a Gm. per kg. basis), the large (1.5 × normal of group on Gm. per kg. basis) and beautifully patterned liver due to excessive leukocytic infiltration along normal interlobular demarcations of pig liver, and the "hobnail" mucosa of the cecum. It may be restated that, except for the cervical lymph nodes, there were no obviously enlarged nodes in the body.—Lieut. Col. B. F. Trum, V. C., U. S. Army, and Lieut. Col. W. T. Carll, U. S. Army (Ret.), Lymphatic Leukemia in a Hog Following Atomic Exposure to Gamma Radiation—A Case Report, *Journal of the American Veterinary Medical Association*, Nov. 15, 1957.

TRAUMATIC PERIOSTITIS IN INFANTS AND CHILDREN

Morris S. Friedman, M.D., South Bend, Ind.

The characteristic etiology and course of traumatic periostitis is illustrated by the case histories of seven children up to 10 years of age. Frequently the traumatic event itself was forgotten until frank disability led to thorough investigation. The symptoms sometimes suggested the paralysis of poliomyelitis, but roentgenograms showed characteristic periosteal lesions, explained the unwillingness of the child to use the affected extremity, and led to recollection of the injury. Spontaneous recovery followed in these traumatic cases. Three other cases are described to illustrate the importance of differential diagnosis. One proved to be infantile cortical hyperostosis, the cause of which is unknown; recovery was spontaneous. The other two were manifestations of scurvy and of congenital syphilis and responded promptly to the necessary specific treatment, which was dietary in the former and antibiotic in the latter.

It is common knowledge that the most frequent skeletal lesions in infants and children are the results of trauma. Usually, there is a history of a definite traumatic episode which is rapidly followed by pain, swelling, and, at times, deformity and immobility of an extremity. The diagnosis is often made before the roentgenogram definitely establishes the presence of a fracture or dislocation. Not infrequently, however, children are seen with roentgenologic evidence of trauma to the extremities when there is no history of injury and trauma is not even expected. The characteristic roentgenographic finding is a mild to marked periosteal reaction around the shaft of a long bone and, at times, a very faint fracture line or epiphysial separation with extensive periostitis.[1] The periostitis may be found in one or more bones or extremities. The true nature of these roentgenographic findings are often not recognized, the findings being mistaken for acute osteomyelitis, scurvy, and even malignant bone tumors.

Snedecor and Wilson,[2] in 1949, reported 11 cases of calcifying periostitis in newborn infants, all of whom were delivered by breech presentation. In almost every one of these infants tenderness and swelling of a leg was noted on the day after delivery. Roentgenograms taken on the second or third day of life were always negative. However, by the 7th or 10th day the roentgenogram showed extensive periostitis in the metaphysis of the long bones in the injured extremity. These authors postulated that the strong manual pull exerted on the infant's legs in the breech delivery causes stripping of the periosteum and subperiosteal hemorrhage; the periosteum later becomes calcified, which shows up in the roentgenogram. The prognosis in their cases was uniformly good. Within two or three weeks the clinical symptoms disappeared and the roentgenograms showed less periosteal thickening.

Barmeyer, Alderson, and Cox,[3] in 1951, reported five cases of traumatic periostitis involving only the lower extremity in young children and infants. In each case, there was tenderness and slight swelling over the thigh or leg and the child limped or refused to bear weight on the leg. Initial roentgenograms were always negative, but 7 to 10 days after onset of complaints an ossifying periostitis appeared in the roentgenogram. Although history of an injury was not always obtained, these authors recognized the roentgenographic picture of periosteal proliferation as the result of trauma and differentiated this condition from other skeletal lesions of early childhood.

Silverman,[1] in 1953, emphasized trauma as the unrecognized cause of certain skeletal lesions in infants. He presented three cases of fractures which had not been suspected clinically as illustrations of "unrecognized skeletal trauma." The striking feature in the roentgenograms of these patients was the extensive periostitis surrounding the bone and the very faint fracture line. In none of the patients was there an adequate history of trauma until the roentgenographic findings indicated the need for a more careful questioning about the possibility of an injury.

Etiology

In the infant and young child, the periosteum is more loosely attached than in the adult and strips off more easily. Even relatively trivial trauma may cause subperiosteal hemorrhage and extensive periosteal stripping.[1] After organization of subperiosteal hematoma, calcification and formation of new subperiosteal bone may be manifested in the roentgenogram. The new subperiosteal bone involves only the shaft and never extends beyond the epiphysial line. In the roentgenogram the "subperiosteal cloaking" may appear as a faint line along the shaft or may be massive enough to resemble

From the Orthopedic Service of the Northern Indiana Children's Hospital, South Bend, and St. Joseph Hospital, Mishawaka, Ind.

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the calcified subperiosteal hematoma of scurvy, depending on the extent of the periosteal stripping. Although a faint fracture line of an epiphysial displacement may be seen in the roentgenogram, these findings are overshadowed by the extensive new

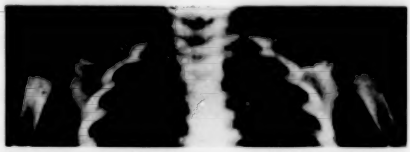

Fig. 1 (case 1).—Periostitis in proximal portion of humerus, bilateral.

subperiosteal bone production. Certainly not all infants and children who are injured develop the clinical signs or the roentgenographic manifestations of traumatic periostitis. Perhaps, as Silverman has suggested,[1] there is an individual factor which predisposes some children more than others to the development of subperiosteal hemorrhage after trauma.

The following case histories illustrate the clinical and roentgenological manifestations of traumatic periostitis and show how this condition may be confused with other diseases.

Report of Cases

Case 1.—A 2-year-old male infant was admitted to the Northern Indiana Children's Hospital on March 17, 1953, with complaints of weakness in both arms and fever. About a month prior to his admission, the child had been acutely ill with an upper respiratory infection and a fever which subsided after penicillin therapy. Several days after this illness, the mother noticed that he could not raise either arm. He was examined by a physician, who made a diagnosis of anterior poliomyelitis in the convalescent stage. Hospitalization was advised, but the patient was not seen again until he was admitted to the hospital about two weeks later. Examination at this time showed a well-nourished but somewhat irritable and listless child. He seemed to have pain in both shoulders and refused to move either arm, although there was no evidence of any swelling, muscle atrophy, or paralysis in either upper extremity. The fever of 101 F (38.3 C) was thought to be due to an ear infection. Cerebrospinal fluid findings were entirely normal, and the blood cell count was normal except for a mild elevation of the leukocyte count (12,000 per cubic millimeter with 56% polymorphonuclear cells). Blood calcium, phosphorus, and phosphatase determinations, vitamin C level, and coagulation and bleeding time were all normal. Antibiotic therapy was instituted, and within a few days the fever subsided and the patient became more alert and less irritable.

A few days after the child's admission to the hospital, a roentgenogram of his chest revealed a normal heart and lungs. The same roentgenogram, however, showed extensive periosteal new bone and proliferation about the proximal shaft of the humerus in both shoulders (fig. 1). A survey of the skeleton showed no abnormalities in any other bone. The patient's condition improved rapidly. By the time he was discharged from the hospital, the 10th day after admission, he was completely afebrile and able to move his arms without pain. Within two weeks after discharge he had regained most of the motion in his shoulders. He was not seen for further examination.

Comment.—After studying the roentgenograms, I attempted to obtain a history of trauma in this case. The mother was unaware of any injury or at least denied it. The whereabouts of the father was unknown. The mother being employed, the child was left in the care of other people most of the day. An impression was gained that the mother had some guilt feelings about the child. Repeated requests to bring the patient in for examination were ignored. Considering the child's environment, it was felt likely that he had suffered some injury or some form of physical punishment at some time before admission to the hospital.

Case 2.—A 17-month-old female infant was brought to her pediatrician on April 14, 1950, with the complaint of "throwing her left leg out when she walked." The child seemed to have no pain and had no fever and no limp. No tenderness or swelling could be found over the left lower extremity. A roentgenogram of the pelvis and both lower extremities showed a faint periostitis around the entire shaft of the left femur. This was interpreted by the roentgenologist as suggestive of a low-grade inflammatory process, such as osteomyelitis, but he added that the possibility of a tumor should be considered. The blood cell count was normal except for a moderately low leukocyte count. A tibial puncture was done, which revealed an entirely normal bone marrow. A roentgenogram of the left femur on April 27 showed an increase in the periostitis and some thickening of the cortex of the femur (fig. 2). On June 13,

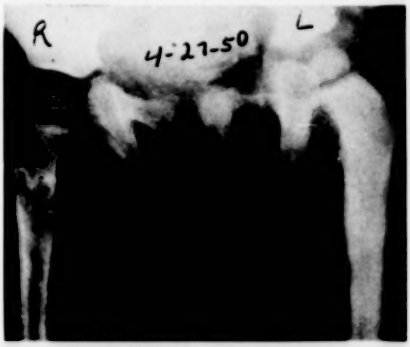

Fig. 2 (case 2).—Periostitis and some thickening of cortex in left femur.

the roentgenogram was reported as showing "beginning healing of the inflammatory process." Final roentgenograms on Sept. 7, 1950, revealed complete disappearance of the periostitis but slight residual thickening of the cortex of the femoral shaft. Interestingly enough, this child sustained a supracondylar fracture of the right elbow about nine months later.

Comment.—There was no history of any injury in this case; in fact, trauma was not even suspected by the child's physician or by the roentgenologist

even after repeated roentgenographic examinations. It was not until three years later, after other cases of traumatic periostitis had been recognized, that the nature of the skeletal lesion in this patient was suspected.

Case 3.—A 2-year-old female child was seen on Oct. 12, 1952, with a painful, swollen left elbow. Five weeks prior to that day the child was injured in an automobile accident when she was thrown against the dashboard. After the accident, the child complained of some pain in the elbow and was reluctant to move the arm. Examination revealed moderate swelling of the elbow, extending from the middle of the forearm to the middle of the upper arm. The elbow was extremely sensitive to palpation, and motion was markedly restricted. A roentgenogram of the elbow showed a rather marked periosteal proliferation about the distal shaft of the left humerus (fig. 3). A mild periostitis was also noted along the entire length of the left radius and ulna. The arm was placed in a sling. Examination a few months later showed that the child had recovered most of the motion in the elbow.

On June 20, 1953, the child was brought to the family physician with a complaint of pain in the shoulder and inability to move the left shoulder joint. The mother at first denied that the patient had been injured, but, when the presence of several bruises on the child's body and arms were called to her attention, she admitted having beaten the child and having pulled it out of the high chair by the left arm several days prior to the examination. A

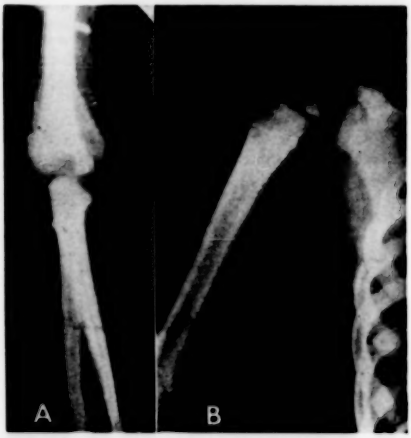

Fig. 3 (case 3).—*A*, periostitis along distal end of humerus, with less marked periostitis along radius and ulna. *B*, mild periostitis at proximal metaphysis of humerus.

roentgenogram of the left shoulder and arm showed a mild periostitis near the proximal epiphysis of the humerus (fig. 3). Examination several weeks later showed that the patient had completely recovered from the shoulder injury. (The poor quality of the patient's environment was again illustrated some months later when the child was admitted to the hospital because of extreme dehydration and malnutrition.)

Case 4.—A 3½-year-old boy was brought to the emergency room of the hospital on Sept. 13, 1954, with the complaint of pain in the left elbow after having fallen out of a swing. Examination of the elbow revealed moderate swelling, some limitation of motion, and slight tenderness. The roentgenograms showed a faint periosteal proliferation along the lower shaft of the humerus; this was thought to be due to

Fig. 4 (case 4).—Faint periostitis at lower end of humerus.

a previous injury (fig. 4). On questioning the mother about any previous injury, it was learned that the boy had fallen about three weeks before and had injured the same elbow. Since the child did not seem to have much pain at the time, he was not taken to a doctor. For several days, however, the boy did not use the arm well. The elbow seemed to improve gradually until he injured it the second time.

Comment.—In this case, a recent injury brought the patient to the hospital. The roentgenogram, however, showed a mild periostitis caused by an earlier injury which was considered too trivial to require treatment. The earlier injury would have been forgotten had not the roentgenograms later revealed it.

Case 5.—An 8-month-old female infant was admitted to the hospital on March 26, 1956, because of a two-day duration of painful swelling of the left shoulder and failure to move the left arm. Two weeks prior to admission the child fell off a chair on her left side, sustaining a bruise on the left side of the face. For four days before admission she had had an upper respiratory infection and fever. Physical examination revealed a well-developed, well-nourished infant who was extremely irritable, especially when being handled. The temperature was 101 F (38.3 C) and her pulse rate 100 per minute. The tonsils were covered with a white, patchy exudate. She would not move her left arm except for slight motion in the fingers. The left shoulder revealed a moderate swelling which was firm and quite tender. The physical examination was otherwise normal. Blood cell count, urinalysis, platelet count, bleeding time, and coagulation time were all normal. Spinal tap and blood culture showed negative results. Throat culture showed nonhemolytic Staphylococcus pyogenes var. aureus. Roentgenograms of the left shoulder showed only some soft tissue swelling. The child was started on antibiotic therapy, and within a few days the fever subsided and the tonsillitis cleared up.

On April 3, 1956, the roentgenogram of the left shoulder showed a fine line of periosteal elevation along the shaft of the humerus. A roentgenogram of the right shoulder was negative. Further roentgenographic examination of the left shoulder on April 10 showed a more marked periosteal proliferation involving the proximal two-thirds of the shaft of the humerus (fig. 5). A skeletal survey showed negative findings. The clinical course over the two weeks of hospitalization was one of slow but steady improvement. On her discharge from the hospital, the child was moving her

V 1
195

left arm as well as the right and had very little tenderness or pain on manipulation, and the swelling had practically disappeared.

Comment.—In this case there was a definite history of an injury about two weeks prior to the child's hospital admission. Although the initial

Fig. 5 (case 5).—Marked periostitis of entire shaft of humerus.

roentgenograms of the left shoulder showed negative results, progressive calcifying periostitis showed up on later examinations. The clinical recovery was almost complete when the roentgenogram still showed considerable periostitis.

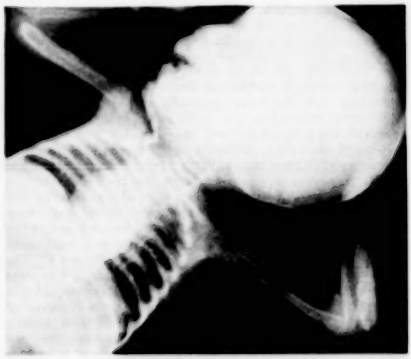

Fig. 6 (case 6).—Marked periostitis in left ulna and mild periostitis in right humerus.

Case 6.—A 2-month-old female infant was seen on Sept. 2, 1955, because of a swelling of the left forearm and immobility of the left arm. Physical examination was negative except for moderate swelling and tenderness over the left forearm and pain on handling. There was no fever. The roentgenogram showed marked periosteal proliferation along the shaft of the left ulna and to a lesser extent of the right humerus (fig. 6). There was no history of any special injury, but the mother, on being questioned, admitted that she had grasped the baby's arms suddenly to keep her from falling several days prior to the onset of the complaints. The baby did not become ill and had no fever later. Within two weeks after the first examination she had recovered full use of her left arm. Examination on Oct. 11, 1955, showed only slight swelling on the ulnar side of the left forearm.

In this case, again, trauma was not suspected until the roentgenogram revealed the skeletal lesion. Furthermore, traumatic periostitis was found not only where there were symptoms (left ulna) but also at a site where there were no clinical manifestations (right humerus).

Case 7.—A 10-year-old boy was seen on May 1, 1956, with the complaint of pain in his left leg. Two weeks prior to his examination, he had fallen while playing in the school gym and several boys had piled on top of him and stepped on his left leg. He did not have any pain until the next day, when he began to complain of an ache in the middle of the lower leg. The intensity of the pain had gradually increased until it began to keep him awake at night. Examination revealed a well-developed, healthy boy who walked with a definite limp on the left leg. There was

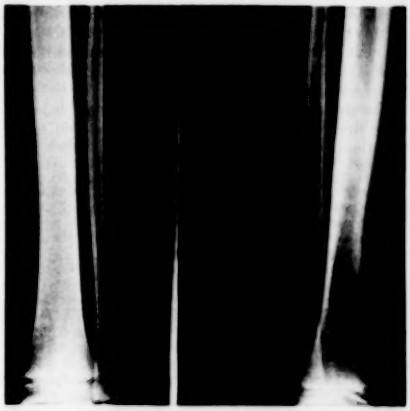

Fig. 7 (case 7).—Faint periosteal line on lateral surface of tibia and increased density in medullary cavity, resembling osteomyelitis or neoplasm.

slight swelling and exquisite localized tenderness to pressure over the anterior surface of the left tibia about 6 in. below the knee. The left calf measured ¾ in. more in circumference than the right. Roentgenogram of the left leg showed a faint line of periosteal elevation on the lateral surface of the middle third of the tibia. There was also an area of increased density in the medullary cavity and irregular areas of rarefaction in the middle of the shaft of the tibia (fig. 7). The patient was admitted to the hospital on May 4 with a diagnosis of possible early bone neoplasm. The roentgenogram was repeated and showed the same changes as described above but somewhat more marked. The roentgenologist's diagnosis was osteomyelitis. Physical examination was essentially negative except for the findings in the left leg. Blood cell count, sedimentation rate, and roentgenogram of the chest were all normal. The child's temperature remained normal. On May 7, a biopsy of the left tibia was done. The periosteum appeared to be thickened and the cortex under it slightly roughened, but no tumor tissue and no pus were found. A smear from the site of the biopsy showed no organisms. The microscopic diagnosis was a "nonspecific fibro-osseous proliferation."

The postoperative course was uneventful. His temperature remained normal, the pain in the leg subsided within a few days, and the patient was discharged with crutches from the hospital a week after the biopsy was done. He made a complete recovery; within a few weeks all the pain and swelling in his leg had completely subsided. On June 19, roentgenograms showed a very fine periosteal line along the entire shaft of the tibia. On Aug. 1, the roentgenogram was entirely normal except for the small defect where the biopsy had been taken. The periostitis had completely disappeared.

Comment.—In this patient the periostitis was not marked, apparently because the child was older and the periosteum more adherent and less proliferative than in infants and younger children. The clinical picture, with the roentgenographic findings of periostitis, sclerosis, and rarefaction, resembled osteomyelitis and even an early bone neoplasm. It was not until after the microscopic sections showed merely periosteal new bone formation and the subsequent benign course of the condition was seen that a definite diagnosis of traumatic periostitis was made in this case.

The following two cases are presented to illustrate the resemblance between the roentgen manifestations of traumatic periostitis and other conditions.

Case 8.—A 3-month-old female infant was admitted to the hospital on July 17, 1956, with a swelling of the left forearm and fever of 10 days' duration. Physical examination revealed a well-developed and well-nourished infant with marked irritability and a temperature of 100 F (37.7 C). The examination was essentially negative except for that of the left forearm, which showed tenderness, swelling, and induration from the elbow to the wrist. Manipulation of this extremity seemed to be painful. The white blood cell count was 23,000 per cubic millimeter, with polymorphonuclear cells 61%. The serum alkaline phosphatase level was 39.9 units per 100 cc. The roentgenogram of the left forearm showed marked proliferation of the periosteum of the entire radius and ulna (fig. 8). A diagnosis of acute osteomyelitis was first considered but then ruled out because of the involvement of both the radius and the ulna. Roentgenogram of the chest and a skeletal survey showed only changes in the left forearm.

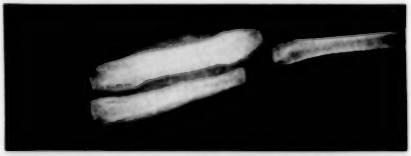

Fig. 8 (case 8).—Marked periosteal and cortical thickening of left radius and ulna and soft tissue swelling; diagnosis, congenital cortical hyperostosis.

In spite of antibiotic therapy the infant continued to run a fever of 100 to 101 F (37.7 to 38.3 C) during her entire hospital stay. The forearm remained swollen and indurated but became less tender. On Aug. 2, almost four weeks after the onset of her illness, a swelling of the left side of the face was noted but roentgenograms of the face showed negative findings. The final diagnosis was congenital cortical hyperostosis (Caffey's syndrome).

Comment.—Roentgenographically, this case bears a strong resemblance to traumatic periostitis. The protracted clinical course, persistent fever, elevated white blood cell count, and elevated alkaline phosphatase level are more consistent with the diagnosis

Fig. 9 (case 9).—Calcification of subperiosteal hemorrhage of both humeri; diagnosis, scurvy (note resemblance to figure 5).

of congenital cortical hyperostosis.[4] The diagnosis was finally established by the appearance of the facial swelling.

Case 9.—A 9-month-old female infant was admitted to the hospital on March 25, 1952, because of a painful swelling of the right shoulder, fever, and irritability. A roentgenogram was taken of the right shoulder and reported by the roentgenologist as showing a fracture through the upper humeral epiphysis. During the first week of hospitalization the child was irritable and apparently unable to move the right arm. A blood cell count showed erythrocytes, 3.8 million per cubic millimeter; hemoglobin, 62%; and leukocytes, 12,900 per cubic millimeter, with lymphocytes, 87%. The urine showed occult blood on repeated examination. Spinal puncture revealed normal findings. The child was given antibiotics, and the fever gradually subsided. However, a week after admission the child was still irritable and screamed when handled, and the shoulder was still quite tender and somewhat swollen. Roentgenograms then showed separation of the capital epiphysis of the right humerus and a faint periostitis at the metaphysis in both shoulders. A skeletal survey a few days later showed irregularity and flaring of the epiphysial lines, rarefaction of the distal femoral metaphysis, and "ringing" of the femoral and tibial epiphysis at the knees. A diagnosis of scurvy was made, and the patient was given large doses of vitamin C. The child's condition rapidly improved, and within a few days the irritability and the tenderness over the extremities disappeared. Subsequent roentgenograms showed increased calcification of the periosteal new bone in both humeri (fig 9). Examination a few weeks later showed that the child had made a full recovery and had regained full range of motion in the right shoulder with no swelling and no tenderness. Final roentgenogram examination on Aug. 2, 1952, showed healing of the bone lesions in both upper and lower extremities.

Comment.—The last case is that of a very young infant in whom the clinical picture could well resemble traumatic periostitis. The roentgenogram, however, readily established the diagnosis.

Case 10.—A 3-week-old male infant was brought to the office on Feb. 21, 1949, with the complaint of not being able to move the left arm. The mother stated that the delivery was rather easy and that she left the hospital

24 hours after the birth of the child. When the baby was 10 days old, the mother noticed that he was not moving his left arm at all. She took the baby back to the doctor who delivered it and was told that nothing was wrong with the child. Examination revealed a fairly well-nourished infant. The upper left extremity hung limply at the side with the arm in internal rotation and the wrist in marked flexion. A diagnosis of birth paralysis was made, and the mother was advised that the child would need an abduction splint to support the left arm.

On March 18, the mother brought the baby back with the complaint that the child was now holding the right arm in the same position as the left. She also stated that the baby had become very irritable and cried excessively on being handled. Examination showed that the baby seemed to have pain whenever the arms were moved and that the right arm also was now held in internal rotation, with pronation and volar flexion of the wrist. There also seemed to be some enlargement of the elbows and wrists. Roentgenograms of both upper extremities revealed irregular "moth-eaten" areas of rarefaction in the metaphysis of the humerus, radius, and ulna, and at both elbows and wrists, as well as periostitis along the shafts of the radius and ulna. Similar changes were noted in the roentgenograms of the lower extremities. A diagnosis of congenital syphilitic osteochondritis was made. The patient was admitted to the hospital and improved rapidly after administration of penicillin. It was later learned from the hospital records that the mother had had no prenatal care and that the result of her Wasserman test was 4+ on her admission to the hospital.

Summary

Traumatic periostitis is a condition affecting the long bones of infants and young children. Injury to the periosteum of these children, even a relatively minor injury, may cause periosteal stripping and subperiosteal hemorrhage followed by calcifying periostitis. Since in most cases of traumatic periostitis trauma is not suspected, often forgotten, or even entirely denied by those responsible for the care of the child, the clinical and roentgenographic manifestations of this condition may be rather perplexing to the physician. The clinical picture may be that of a pseudoparalysis of an extremity, resembling poliomyelitis or congenital syphilis. Swelling, localized tenderness, reluctance to move an extremity, and excessive sensitiveness to being handled may suggest scurvy. The roentgenographic manifestations of traumatic periostitis may in themselves prove puzzling to those who are not aware of this condition. A lesion may even be revealed in the roentgenogram at a site in which there are no clinical manifestations. The resemblance between traumatic periostitis and congenital cortical hyperostosis in the roentgenogram is striking, and local swelling, tenderness, and periostitis may be difficult to differentiate from acute osteomyelitis or a bone tumor. Since traumatic periostitis is a relatively benign disease which subsides clinically within a few weeks and rarely leaves residual manifestations even in the roentgenogram, it behooves us to be cognizant of its existence and to differentiate it from skeletal lesions of a more serious nature.

105 E. Jefferson Blvd. (1).

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ECONOMIC ASPECTS OF REHABILITATION.—In a nation of 170 million people, we have a total labor force of between 65 and 70 million. It is estimated that there are at least two million handicapped men and women in our country who have a chronic disease or long-term physical or mental impairment that is a substantial deterrent to their employment and which could be overcome by comprehensive rehabilitation services. This group grows, I am told, at the rate of a quarter-million persons each year.

With proper rehabilitation services, and with the qualities of courage and inspiration that make them truly an exceptional group, a large percentage of these can be enabled to engage in remunerative work. With the help of modern scientific rehabilitation, they can be added to the rolls of constructive, tax-paying, contributing Americans. They can be self-supporting members of the national community, more than repaying through their services the outlay government may make to the public assistance programs. I have been informed, for example, that the earnings of handicapped persons rehabilitated under the State/Federal program in 1955, during the first year after their rehabilitation into satisfactory employment, is estimated at $105.1 million. It will interest a public, which presently is more than usually budget and tax conscious, that these persons will pay more in Federal income taxes in three years than the Federal government spent for basic support of the vocational rehabilitation program in 1955.—G. Kirk, Rehabilitation—Its New Day, Rehabilitation Series 22, Institute for the Crippled and Disabled, New York, 1957.

COMPARATIVE STUDY OF CHLORPROMAZINE AND INSULIN COMA IN THERAPY OF PSYCHOSIS

Max Fink, M.D., Robert Shaw, M.D., George E. Gross, M.D.
and
Frederick S. Coleman, M.D., Glen Oaks, N. Y.

The effectiveness of chlorpromazine was compared with that of insulin coma in 60 patients referred for insulin coma therapy. One-half the group, selected on a random basis, received chlorpromazine by mouth for at least three months in doses adjusted so as to fall just short of toxicity in the individual patient; this dosage varied from 300 mg. to 2,000 mg. daily, with a median of 800 mg. The insulin coma was induced by a standard technique 50 times in each patient. Although many minor differences were noted in comparing the effects of these two methods of treatment, the ultimate results at the time of discharge were essentially the same for the two groups of patients. Neither treatment affected the basic schizophrenic process, but chlorpromazine had the advantage of being safer, easier to administer, and better suited to long-term management.

With the advent of "newer" drugs for the treatment of psychiatric illnesses and the concomitant awareness that the effectiveness of insulin coma therapy was limited, a control drug therapy–insulin coma study was undertaken. Preliminary trials with various medicaments available in 1954 demonstrated chlorpromazine to be potent and relatively safe. Concurrent reports had noted its value in schizophrenic illnesses, and it was therefore selected as the experimental agent.

The study was designed to assess the therapeutic efficacy and indications for intensive chlorpromazine therapy, compared to classic insulin coma therapy, an in open-ward, voluntarily hospitalized psychiatric population.

Subjects and Method

All patients referred for insulin coma therapy during the period Sept. 1, 1955, to Dec. 31, 1956, were observed. Supervising psychiatrists made the recommendation for insulin coma therapy independent of the research group. Their criteria for referral were those implicitly held by the hospital administration and were not altered for this study. Randomly selected patients were placed on chlorpromazine therapy instead of insulin coma therapy. This selection was made by the psychiatrist in charge of the insulin therapy unit without prior notice of the referring therapist or the supervising psychiatrist. Sixty patients were referred for insulin coma therapy during the study period, and half of these received chlorpromazine.

Insulin Coma.—The standard technique of Sakel for insulin coma was used. All patients received 50 comas, each of a duration of at least one hour, at the physiological level of Babinski reflex, absent lid reflex, or deeper. Recovery was induced by gavage and occasionally by intravenous administration of glucose. Treatments were given five times weekly for a period of three to four months.

Chlorpromazine.—To establish an equivalent group, chlorpromazine was given for at least three months. Dosages were determined by the research team and were rapidly increased until well-defined physiological effects were observed. These included rigidity, drooling and fixed facies, seizures, or severe dermatitis. In most instances this was achieved below 1,400 mg. daily, although dosages were increased to 3,600 mg. in one patient. In each instance, the drug dosage was slowly reduced until a maintenance dose, just under that producing toxicity, was obtained. This varied from 300 mg. to 2,000 mg. daily with a median of 800 mg.

To determine the comparability of the subjects in the random sampling procedures used in this study, the groups were compared as to their psychiatric diagnoses and ages. Table 1 shows a comparison of the groups as to diagnoses and demonstrates an equal distribution of subjects in each category. In the analysis of the age distribution, the median age for patients subjected to insulin coma was 24 years, with a range of 17 to 38; the median age for patients receiving chlorpromazine was 28, with a range of 19 to 42. Here, too, the distribution shows no significant difference.

For both treatment groups, behavioral observations were made by the research staff at weekly intervals. After completion of the treatment period, reports of the patients' behavior were obtained from the therapist and supervising psychiatrist. The "improvement" rating was determined by the medical director at the patient's discharge conference and was based on the fourfold scale of recovered, much improved, improved, and unimproved. Neither the authors nor the supervisor of the insulin therapy unit participated in these evaluations.

From the Department of Experimental Psychiatry, Hillside Hospital.

Observations

Clinical Observations.—The following clinical effects were noted in patients who received chlorpromazine and in those subjected to insulin coma therapy.

Chlorpromazine: Chlorpromazine induced motor retardation in all subjects. Overactive, destructive behavior rapidly disappeared, and patients became more tractable, less negativistic, and less violent. The nurses' and therapists' records noted patients as "less easily excited and frightened," "cooperating better in ward activities," and "less restless and less panic-ridden." One-third of the patients were more sociable and less seclusive and were noted to care for themselves in a more presentable fashion. In instances where severe motor symptoms supervened, however, the patients were less able to care for themselves; they became sloppy and failed to dress themselves. Such periods were usually short and could be significantly modified either by a reduction in drug dosage or by anti-Parkinsonism drugs.

TABLE 1.—*Psychiatric Diagnoses*

	Insulin Coma	Chlorpromazine
Psychoneurosis	1	2
Schizophrenia, paranoid	10	10
Schizophrenia, catatonic	7	7
Schizophrenia, mixed	8	6
Schizophrenia, hebephrenic	3	2
Manic-depressive psychosis	1	3

Affective changes during chlorpromazine treatment were varied. Four patients became increasingly agitated, tense, and tremulous and either refused to continue on the drug regimen or were induced to do so only with difficulty. Such an affective "storm" appeared early in the treatment and persisted. In four other patients, depressive symptoms were relieved with an increase in affective lability and responsivity. Depressive ideation increased, associated with complaints of insomnia and anorexia in two patients. The medication was continued, however, with an eventual alleviation. In most patients, mood changes were small.

Ideation was dramatically altered during the period of chlorpromazine therapy in 12 patients. Eight had a loss or a significant diminution of their psychotic ideation. In five, hallucinatory and referential experiences were no longer reported even on inquiry, and, in three others, delusional ideas were less prominent. In one patient, phobias were relieved and the patient could once again participate in ward activities. In another, hypochondriasis was sufficiently modified to permit a more meaningful relationship between therapist and patient. In one patient, paranoid ideation became more prominent. This was associated with increasing anxiety and panic during drug administration and resulted in discontinuation of the drug regimen.

Insulin Coma: The clinical observations in this group were similar to those reported by others.[1] Alteration in behavior was prominent in all patients once repeated comas were induced. Overactive, hostile behavior rapidly diminished and was replaced by alternating periods of somnolence, irritability, and withdrawal. In most patients, nausea, abdominal distress, belching, sweating, and lassitude were common sequelae each afternoon and assumed prominence in the recorded reports. These symptoms often interfered with the patients' ability to care for themselves, and they became unkempt in their dress.

Changes in ideation appeared slowly during the course of therapy. In eight patients, paranoid and delusional thoughts became less prominent, disappearing in these on direct inquiry. Suicidal and outwardly directed destructive thoughts were modified in three patients, only to recur in each at the end of the treatment period.

Mood changes were small. Increasing agitation, tension, and panic were reported in three patients, leading in two to a refusal of further therapy. In one depressed patient, relief of depressive symptoms was noted early in the treatment and was sustained.

In the usual practice of the treatment unit, concurrent electroconvulsive therapy was instituted when behavioral control by insulin coma alone was limited. In six patients, such combined treatment was instituted primarily because of a continuation of overactive or delusional ideation. There was, in four instances, a well defined alteration in behavior, but this was unsustained. None of these patients was rated as improved on discharge.

Discharge Evaluation.—All patients were discharged from the hospital within four months of the end of treatment. Table 2 lists the hospital discharge evaluations for patients treated with chlorpromazine and insulin coma.

TABLE 2.—*Discharge Ratings in Patients Treated with Chlorpromazine and Insulin Coma*

	Treatment	
	Chlorpromazine	Insulin Coma
Recovered, no.	2	0
Much improved, no.	4	5
Improved, no.	17	15
Unimproved, no.	7	10

Included in the group of patients treated with chlorpromazine who were rated as unimproved were four who received inadequate course of therapy (less than one month) because of complications of the therapy. Of the 10 patients treated with insulin coma who were rated as unimproved, four had inadequate courses of therapy, two because of complications (seizures and prolonged coma), one because she became more disturbed, and one because of administrative transfer to another facility.

It is apparent that there is no difference in the clinical evaluation at the time of discharge between the group receiving insulin coma and that receiving chlorpromazine. To determine whether this sample was biased because of its small number, we compared these discharge ratings with a similar group treated in this hospital in 1950 and previously reported.[3] In table 3, the discharge ratings for both

TABLE 3.—*Discharge Ratings Compared for 1950 and 1956*

	Present Group (30 Subjects)	1950 Group (48 Subjects)
Recovered, %	0	14
Much improved, %	17	19
Improved, %	50	42
Unimproved, %	33	25

years are compared. The percentage improvement rates for each category are not significantly different.

Toxicity and Complications.—Patients receiving chlorpromazine and those subjected to insulin coma therapy were compared as to toxic reactions and complications, with the following effects noted.

Chlorpromazine: Inherent in the design of this study were high doses of chlorpromazine, pushed to a level producing symptoms of toxicity. In this context, all patients developed significant drug effects. Rigidity of extremities, accompanied by a decrease in facial expression, drooling, and festination, was frequently observed. In three instances, rigidity appeared as drug dosage was reduced. Most patients became drowsy, retarded, and less active in ward activities. In four patients increased tension, agitation, restlessness, and excitement supervened, leading to a discontinuation of the drug regimen in two.

Seizures occurred spontaneously in three patients. Pretreatment electroencephalograms had manifested no dysrhythmia, and no history of seizures had been elicited. In each, the drug medication was reduced, and seizures did not develop at the lower dosages.

Dermatitis was a frequent complication. All patients developed a transient erythema to mild solar radiation. Severe intractable skin reactions occurred in three patients, with resultant discontinuation of drug therapy in two. In the third, promazine hydrochloride therapy was substituted for chlorpromazine, with a relief of the dermatitis. The behavioral effect of the promazine was indistinguishable in this patient from that noted in patients receiving chlorpromazine.

In this group, no patient developed clinical jaundice. This complication has been variously reported as occurring in less than 0.5% of subjects treated. In the preliminary studies at Hillside Hospital, 3 patients of a group of 20 developed transient clinical jaundice.

Electroencephalograms were obtained in 20 of the patients who received chlorpromazine. With increasing doses, the modulation of the record became more irregular in each. A moderate amount of low-voltage 4-7 cps delta and theta activity was induced, and this activity was exaggerated by hyperventilation. There was a suggestive relationship between the degree of the induced slow-wave activity and the drug dosage.

Insulin Coma: The complications of insulin coma therapy in this series were not unusual. Insulin resistance was noted only once and was eventually overcome by the method of alternating dosages. Prolonged reactions occurred in three patients. In each, neurological examination and electroencephalography demonstrated signs of persistent central nervous system dysfunction for at least 10 days. Aphasia, hemiparesis, and paresthesias were frequent in five patients and transient in eight others. Seizures occurred in five patients and were recurrent in three. Frequent secondary reactions, nausea, vomiting, abdominal distress, sweating, pallor, lassitude, and generalized weakness occurred in all patients with varying frequencies.

The complications of both forms of treatment are listed in table 4. Certain effects, such as dermatitis and hypotension, secondary reactions, and prolonged coma are individual for each therapy, and seizures, agitation, and refusal of therapy were noted with both regimens. The frequencies of these are not significantly different.

Effects on Psychotherapeutic Relationship.—Patients were referred for insulin coma therapy after a period of verbal relationship therapy. Such referral implies a failure of interpersonal communication.

TABLE 4.—*Complications of Treatment with Chlorpromazine and Insulin Coma*

	Treatment	
	Chlorpromazine	Insulin Coma
Agitation and panic	4	8
Dermatitis, severe	3	...
Seizures	3	5
Refusal of further therapy	2	2
Hypotension	2	...
Secondary reaction, frequent	...	5
Prolonged coma (>6 hr.)	...	3
Insulin resistance	...	1

Chlorpromazine: During the period of effective drug action, 15 of the patients treated with chlorpromazine were described by the therapist in response to an inquiry as "more accessible," "speaking more freely," and "more amenable to psychotherapy." The behavioral changes could be classified in two groups: subjects in whom tension and preoccupation with somatic symptoms became much less, and those in whom hallucinatory or delusional preoccupations ended. Such changes in

relationship were frequently described as an increase in "contact." In 13 subjects, psychotherapy either was still "not feasible" or had become less feasible because of increasing uncontrolled tension, anxiety, or preoccupation with the side-effects of the drug regimen.

Insulin Coma: Similar observations were made in the patients treated with insulin. Of the 30 patients, 7 were noted to be less tense and less anxious during therapeutic sessions. The therapists noted that the patient "verbalized more freely" and "was more aware of his environment." Four patients were specifically treated with a "modified anaclitic" approach. In each instance, this relationship was unsustained during treatment and the therapists resorted to more conventional tactics. In the remaining patients (19), while supportive, educational, and environmental manipulating techniques were applied, the therapists were no more successful than prior to insulin therapy. In 11 patients, the physiological effects of the treatments (secondary reactions, sweating, nausea, vomiting, and weight gain) were reported as interfering with psychotherapeutic attempts.

Comment

Clinical Considerations.—In these patients, neither chlorpromazine in high therapeutic doses nor insulin coma specifically modified the psychotic process. Since 88% of these patients had a diagnosis of schizophrenic illnesses, we concluded that neither treatment has a specificity in altering the schizophrenic process. When given in adequate dosage, however, both treatments are potent methods for the alteration of behavior. In the discharge evaluations, the treatments are similar. In only 20% of the patients were induced behavioral patterns persistent, with the rating "much improved" or "recovered." For the others, the induced behavioral changes were transient or minimal.

Since these therapies fail to induce a recovery from the psychotic process, consideration should be given to their ameliorative, palliative, and supportive aspects. Symptomatic relief was frequent but generally limited to the treatment period. Patients were made uncomfortable by both therapies, however, and the complications and toxic effects have already been noted.

In assessing the role of concomitant psychotherapy, there is little advantage in either therapy. Both methods were said to enhance relationship therapy, although the therapists' evaluations favored chlorpromazine therapy. Excluding those who developed increased agitation, patients were more comfortable, more alert, and physically better able to discuss their feelings and experiences while on chlorpromazine treatment. It is clear that "interpretive" psychotherapy is not enhanced; rather, supportive, educative, reorienting, and directive types of therapy are. When there is a modification of agitated, hallucinatory, depressed, manic, or aggressive behavior, both the therapist and the patient are more comfortable and better able to discuss the reality aspects of the life situation.

Therefore, in this context, the ease of administration and the possibility of continued maintenance of chlorpromazine in an outpatient setting assume decisive significance. To maintain such therapy after discharge and continue thereby the relationship established in the hospital setting may be an important element in sustaining the behavioral changes induced by hospitalization.

Other Studies.—While many reports of the treatment of psychosis by chlorpromazine have appeared, we are aware of only one similar comparative study. Boardman, Lomas, and Markowe,[3] after a review of the problem, reported a study of 100 patients randomly divided into two groups of 50 and treated with either insulin coma or chlorpromazine. The chlorpromazine dosage was lower than that used in the present series (average 300 mg.), but the drug period (three months) was the same. Their observations are directly comparable to this study. They reported no difference either in discharge evaluations or in symptom assessments for either treatment group.

The patients treated with chlorpromazine, however, remained in the hospital an average of 6.2 weeks less than the subjects treated with insulin. This was a significant difference between the groups. They concluded, "There is inconclusive evidence that chlorpromazine has advantages over insulin in the treatment of schizophrenia [but] insulin has disadvantages in the form of greater danger and more unpleasantness for the patients and greater strain on the nurses. Chlorpromazine is the first treatment of choice in schizophrenia, but this conclusion is based on the immediate results of treatment and has not yet been confirmed by an adequate follow-up study."

Boardman and his co-workers emphasize the problem of evaluating the therapeutic efficacy of insulin coma. They note a number of reports that raise doubts as to the efficacy of insulin coma therapy in schizophrenia. Bourne,[4] in an extensive review of the merits of insulin therapy in schizophrenia, concluded, "There is no proof of any specific therapeutic effect, and the long term prognosis is in no way influenced."

The recent observations of insulin treatment of schizophrenia by Ackner, Harris, and Oldham[5] are relevant. In a carefully controlled study, young schizophrenic patients were randomly treated either by insulin or by barbiturate coma in the same ward and under similar conditions. Evaluations of results were made by psychiatrists without knowl-

edge of which treatment the patients received. The authors noted a similar outcome, whether the loss of consciousness was induced by a barbiturate or by insulin, and concluded that insulin was not a specific therapeutic agent in the outcome.

In the follow-up studies done in this hospital,[2] the therapeutic results of insulin coma therapy were disappointing. Patients referred for insulin coma had the longest period of hospitalization (6.5 months, as against 6.04 with psychotherapy and 4.95 with electroshock), the poorest discharge rating (33% recovered and much improved as against 63% with psychotherapy and 67% with electroshock), and, within four years, a 50% rehospitalization rate (compared to 33% with psychotherapy and 29% with electroshock). While these observations reflect the idea that the more severely ill patients are referred for insulin coma, they also support the belief that insulin coma is not a specific treatment for the patients referred.

From these reports we would conclude that, despite considerable study and the passage of many years, insulin coma therapy has not been shown to induce persistent behavioral changes more frequently than other nonspecific, less dangerous, and less expensive therapies. To the list of alternate therapies of limited value in the management of psychosis we may now add chlorpromazine, noting, however, its advantage of lesser risk and ease of administration.

Dosage of Chlorpromazine.—For the purpose of assuring an adequate level of chlorpromazine dosage for evaluation, the amount of medicament given was increased in all subjects to toxic levels. This level was too high for its behavioral effects, as evidenced by the reduction in all responsive cases to maintenance levels of 300 to 2,000 mg.

It is our impression that chlorpromazine affects the function of the central nervous system (as evidenced by changes in modulation and per cent time delta in the electroencephalogram and the systemic phenomena of rigidity and lassitude) and results in a nonspecific alteration in behavior.[6A] Such behavioral change is varied and is dependent on a variety of factors, of which the personality organization and the expectancy of the milieu are significant. In this context, the induction of a state of altered cerebral function is a necessary prerequisite to behavioral change. The only assurance of achieving a therapeutic level, therefore, is the appearance of toxicity and a lowering of dosage from that level to a maintenance dose. The effects of rigidity, drowsiness, and lassitude, therefore, are necessary concomitants of the therapy and should be induced in all patients in whom a therapeutic effect is desired. In instances where an affective "storm" supervenes, continuation of therapy at higher levels, with concomitant administration of trihexyphenidyl hydrochloride (Artane) and benztropine (Cogentin) methanesulfonate should be considered. Such an attitude in therapy is comparable to the application of digitalis in cardiology and to the present concept of the mode of action of electroshock therapy.[6]

Summary

In a study of patients referred for insulin coma therapy in an open-ward, voluntary psychiatric hospital, patients received randomly either insulin coma therapy or intensive chlorpromazine therapy. Chlorpromazine was found to be as effective in modifying psychotic behavior as insulin coma therapy. There was no difference in the improvement rating on discharge, incidence of complications, or effects on the psychotherapeutic relationship for either therapy.

In comparison to insulin coma, chlorpromazine is safer, easier to administer, and lends itself to long-term management. Patients receiving chlorpromazine therapy are more comfortable than those receiving insulin coma. No evidence has been educed that either therapy has altered the basic schizophrenic process, nor is there any evidence that there is greater specificity of either form of therapy for schizophrenic illnesses.

75-59 263rd St. (Dr. Fink).

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The chlorpromazine used in this study was supplied as Thorazine by Smith, Kline & French Laboratories, Philadelphia.

The promazine hydrochloride used in this study was supplied as Sparine by Wyeth, Inc., Philadelphia.

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V 1
195

TUBERCULOSIS IN KOREA—A CONTROL PROJECT

Ernest B. Struthers, M.D., D.P.H., D.T.M. & H., Seoul, Korea

A program sponsored by Church World Service was developed to aid the Korean people in efforts to control tuberculosis. It included plans for chest clinics, free diagnostic and therapeutic x-rays, sanatorium beds, education of professional personnel and the public, and visits of especially trained nurses to patients' homes. The disease was found to be far advanced in 34% of the first 1,000 patients on their first visit to the clinic. The record of the first 1,000 home visits showed that there were 650 families that had only one room. Of the 163 families occupying a single room each, 23 consisted of from 6 to 10 persons. The treatment usually prescribed was the daily oral administration of isoniazid (3 to 5 mg. per kilogram of body weight) and p-aminosalicylic acid (10 to 12 Gm.). In addition substantial help with food and housing was necessary. It was estimated that 5% of the patients became worse during treatment, but in 59% of an unselected series of 162 patients cultures of sputum no longer yielded tubercle bacilli after six months of treatment (67% after one year). This pilot project showed that the treatment of tuberculosis by the foregoing methods, especially if accompanied by relief measures, is successful with the majority of sufferers from this disease.

It is well known that countries in the Far East have a very high incidence of tuberculosis, but in none of the large countries are methods of diagnosis for the general population of sufficient accuracy to determine the number of active cases nor the death rate. The estimate, therefore, of an annual death rate of 400 per 100,000 of the population in Korea is only a guess. This may be compared to 8.3 per 100 000 for the United States, 7.8 for Canada, or 12.1 for England and Wales. As a result of recent surveys on a small scale, the incidence of active pulmonary tuberculosis appears to be from 2 to 2.6% of the population, although the rate is probably a little lower in country districts.

Since South Korea has a population of over 20 million, there are probably 400,000 who require treatment. Existing beds in sanatoriums and beds available in general hospitals can provide accommodation for only 4,000 patients. In the United States, for an equal number of patients with active disease in a population of 172 million people, there are 125,000 beds in sanatoriums. Health surveys made some years ago for the World Health Organization, the U. S. Army, and the Economic Cooperation Administration, all stated that the most serious disease in Korea is tuberculosis. At that time there were no chest clinics and only 1,000 beds available in sanatoriums.

Initiation of Program

Owing to the concern which mission boards in the United States felt regarding the need of the Korean people for help in the control of this disease, I was asked to initiate a program sponsored by Church World Service, which represents the social service work of over 20 protestant denominations. A budget of $50,000 was recommended. The plan of attack was based upon methods that have proved successful in the West, namely (1) the provision of chest clinics easily available to the public; (2) free x-rays and free treatment; (3) the provision of sanatorium beds, especially to provide facilities for lung surgery; (4) the education of doctors, nurses, and the public; and (5) visits to the homes of patients by graduate nurses specially trained in tuberculosis control.

In January, 1954, a chest clinic was begun in Seoul at Severance Union Medical College Hospital. The aim was to provide a free clinic service with home visiting by graduate nurses as an essential part of the program. In the beginning it was difficult to get nurses to undertake the visiting of patients with tuberculosis, as this was a new type of work.

In the first month there were only 7 patients, but, as these patients told others, in six months the attendance had risen to over 50 a day. This rapid increase in numbers was due to the provision of free x-rays and free treatment for all poor patients. Previously few of these patients could afford to attend a hospital or pay for the x-ray examination or drugs. Poor families were also supplied with clothing and food. This added, no doubt, to the popularity of the clinic, for at the end of 1956, 822 patients were in regular attendance; the average number of daily visits was over 100, and on some days over 180 attended the clinic.

Other clinics were opened in Seoul, and the staff was gradually increased to cope with the increased amount of work. These were at the Red Cross Hospital (begun in August, 1954), Seoul Women's

Professor, Department of Medicine, Severance Union Medical College, and Director, Korea Church World Service Tuberculosis Control Project, 1953-1957.

Medical College Hospital (begun in November, 1954, and continued for one year), City Hospital (May, 1955), Sun Hwa (November, 1956), and Yung Dong Po (February, 1957). With the exception of Severance, which is a private hospital assisted by American, Australian, and Canadian missionary societies, and the Red Cross hospital, the other clinics have been set up in government charity hospitals. The government has generously provided quarters and supplied a large portion of the drugs and x-ray films.

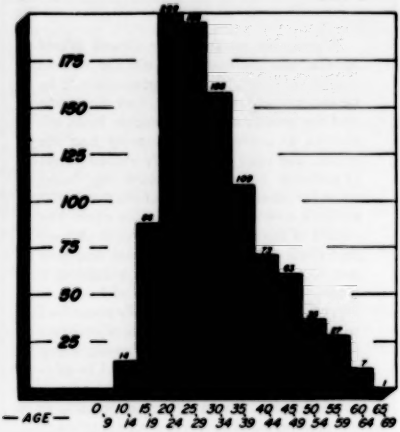

Fig. 1.—Age distribution of 976 adult patients.

When the first clinic was started, there were no male doctors available, as all men on graduation are assigned to the Army, Navy, or Air Force. It was therefore necessary to find and train women graduates. Our staff in Seoul now consists of five women doctors and five men, three of whom have recently returned from postgraduate experience in the United States. The program remains essentially a training program. Twelve nurses are employed in Seoul for home visiting and the work of the clinics.

Beginning in November, 1954, clinics were begun at Sapkyo, Taegu (population about 170,000), Taejon (100,000), and Chongju (52,000). Assistance was given to clinics at Inchon (215,000), Kwangju (100,000), Mokpo (103,000), and Yongin. Clinics at Inchon, Taejon, Kwangju, and Mokpo were associated with mission hospitals; the Taegu clinic was in a government medical college hospital. The Yongin clinic was a village community project. In the village of Sapkyo the clinic was organized, staffed, and completely supported by Korea Church World Service. The staff in Sapkyo consisted of one American nurse, two Korean nurses, and for a time a Korean doctor. The work of the clinic was supervised by Dr. Burgess from the central clinic in Seoul. In two and one-half years 399 patients were under regular treatment. Patients came from a distance of 50 miles, and, although an attempt was made to restrict the service to the district for which it was intended, this was found difficult.

Findings and Procedures

Incidence.—From the study of 1,000 adult patients, it appears that men and women are probably equally affected, although more men than women attend all clinics. Most of those affected are between the ages of 15 and 40 years, with the peak at 25 years (fig. 1). Children at Severance were treated in the pediatric department and so could not be included in this analysis.

Classification.—The disease in the first 1,000 patients on their first visit to the clinic was minimal in 22%, moderately advanced in 44%, and far advanced in 34%.

Overcrowding.—The degree of overcrowding must be seen to be appreciated. An analysis of the home-visiting records for the first 1,000 homes (in which there were one or more persons with pulmonary tuberculosis) visited showed that there were 650 families (65%) that had only one room per family. For 163 families this room was 6 ft. square, and 23 of these families had from 6 to 10 individuals in each family. There were 221 families with two rooms, 96 with three, 24 with four, and 9 (less than 1%) with five or more rooms. Figure 2 shows the number of rooms per family, and figure 3 shows the area of living space per family.

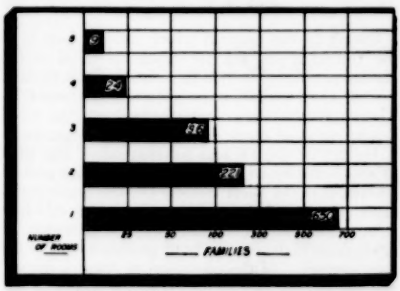

Fig. 2.—Number of rooms per family.

In Korean homes members of the family live and sleep on the floor. Even when there are several rooms in a house, the family during the winter will crowd into the room which has a warm floor. To provide heat for the home, the kitchen is placed outside and at a lower level than the house itself. It is then possible for the flue from the kitchen to pass under the bedroom. In only a few homes is isolation of the patient possible.

Family Income.—Family income in 1,000 families varied from nothing to over $53 a month (fig. 4). There were 72 families whose income was not over $6 a month, and if illness affected the wage-earner this dropped to zero. Twenty-five families had an

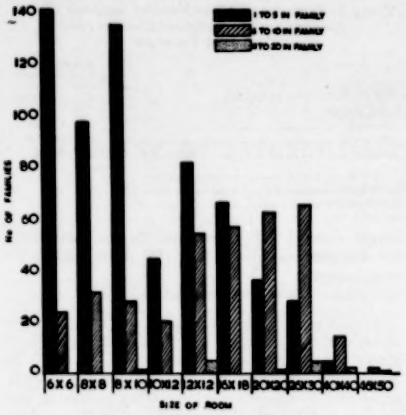

Fig. 3.—Area of living space per family.

income of not over $12, 63 not over $18, and 133 not over $23. Thus there were at least 293 families of 1,000 who were living at semistarvation level. Over half (51%) had an income not exceeding $33 a month. No data are available as to what proportion of the families in the city who do not have a patient to care for exist at this level.

Education.—A booklet, "Instructions for Patients," has been prepared in Korean and a copy given to each patient, most of whom are able to read Korean phonetic script. A series of talks and dialogues has been broadcast from two radio stations, and articles have been supplied to the newspapers by members of the staff.

Home Visiting.—Home visiting is an essential part of the program, since few families know the infectious nature of the disease. Also, patients who are visited in their homes follow instructions better than those not visited. Each nurse works under the supervision of a clinic doctor and instructs the family regarding methods of transmission, the importance of complete rest when this has been ordered (about half follow instructions), and the value of good food, fresh air, and sunlight. Contacts are urged to come to the hospital for a free chest x-ray. The nurse also records the condition of the home, the number and size of the rooms, the economic status of the family, and whether clothing, food, or cash are most needed. Weekly conferences are held on problems disclosed in these visits. In Seoul, 2,747 homes were visited and 6,147 return visits made. There were 4,199 homes visited and 13,934 return visits at all clinics, including those outside Seoul.

Relief.—About 10 tons of food supplies were issued each year to patients. The bulk of these supplies was from Korea Church World Service, the Mennonite Central Committee, and United States and Canadian Army chaplains. Seventy families were given small cash grants at various times, and 12 destitute patients were given the equivalent of $8 a month for over a year. The United Church of Canada supplied $3,000 for this relief. Much more could have been done had larger sums been available. In 1904, in Edinburgh, Sir Robert Philip stated his belief that in the solution of the tuberculosis problem a plan of supervised relief must play a chief part.

Shelters.—Prefabricated wood shelters have been designed for patients whose disease remains infectious after prolonged treatment and who are unsuitable for lung surgery. A number of these have been loaned to families and erected close to the homes.

Eighth Army Memorial Chest Hospital.—As part of the project for the training of doctors, students, and nurses and especially to provide facilities for chest surgery, a hospital of 140 beds is under construction in Seoul. Materials for the building and its equipment have been supplied by the U. S. Eighth Army. When finished the hospital will be administered as part of Severance Hospital.

Treatment and Results

Treatment.—The treatment usually prescribed is the daily oral administration of isoniazid (nicotinic acid hydrazide), 3 to 5 mg. per kilogram of body

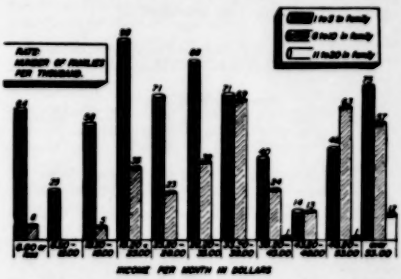

Fig. 4.—Income in families where member has pulmonary tuberculosis.

weight, and 10 to 12 Gm. of PAS (*p*-aminosalicylic acid). Streptomycin, 1 Gm. injected twice a week, may be added or may replace isoniazid. Usually either isoniazid or streptomycin is used, not both, especially in patients who might sometime become candidates for thoracic surgery. Our impression is

that isoniazid gives slightly better results than streptomycin. An analysis of the results in a large series is in preparation.

About 1.5% of those attending the clinics showed x-ray changes which were proved to be due to paragonimiasis. Paragonimus westermani eggs were found in the sputum. Approximately 25% of those who attended the clinic for an x-ray examination showed radiologic signs consistent with a diagnosis of active pulmonary tuberculosis. At the end of 1956, 1,500 patients were under treatment in Seoul and 2,500 additional patients in other centers. A summary of data is given in table 1.

Results

Results in an unselected series of 162 patients showed that, after three months' treatment, in 32% of the cases the sputum showed no evidence of tubercle bacilli on culture; after six months the percentage was 59, after nine months months 63, and after one year 67. Table 2 gives an analysis of results in a small number of patients treated, but the results in the large series are similar.

In Sapkyo, a country village, where many of the patients were farmers who insisted that to keep their families from starvation it was necessary to continue to work their farms, the results were not as good as in clinics where a larger proportion of patients were able to rest; nevertheless, the results were better than was expected.

Dr. John N. Burgess reported the results in 161 patients. The lesions, as assessed by x-ray examination before treatment, were far advanced in 93 patients, moderately advanced in 50, minimal in 77, primary in 6, and miliary in 4. Of the 143 patients with far-advanced and moderately advanced disease, most had had symptoms over six months, and many had had previous treatment.

TABLE 1.—*Summary of Data on Persons with Pulmonary Tuberculosis in 1954, 1955, and 1956*

	Data from Clinics at Seoul								Data from All Clinics	
	1954		1955		1956		Total			
	No.	%	No.	%	No.	%	No.	%	No.	%
Persons x-rayed, no.	4,517	100	6,980	100	6,982	100	18,479	100	27,280	100
Active	1,019	22.8	1,636	23.3	1,801	26.2	4,476	24.2	7,655	28.1
Questionable	42	0.9	115	1.6	102	1.5	259	1.4	695	2.5
Inactive	78	1.7	114	1.6	77	1.1	269	1.4	499	1.8
Suspect	159	3.5	73	1.0	57	0.8	289	1.5	413	1.5
New homes visited	470	...	1,233	...	1,044	...	2,747	...	4,199	...
Return visits to homes	746	...	2,558	...	2,883	...	6,147	...	13,504	...

After treatment, x-ray changes indicated improvement in 65% of these patients; improvement was marked in 64, moderate in 33, and slight in 8 patients. There was no change in 48, or 30%. Deterioration occurred in 8, or 5%.

In this series of 161 patients, 40 had had less than eight months' treatment. It was thought that eventually 80% would show improvement. Only 22%, however, showed a change of positive to negative sputum, although those whose treatment was longer showed 33% conversion. In the same series Dr. Burgess considered that 15% were suitable for lung surgery.

TABLE 2.—*Percentages of One Hundred Sixty-two Patients Showing Various Radiologic Changes After Beginning Treatment*

Type of Change	No. Months After Starting Treatment			
	3	6	9	12
Improvement				
Marked	13	26	31	45
Moderate	9	21	26	16
Slight	37	35	30	21
Total				82
No change	35	16	14	13
Deterioration	6	2	6	5

Comment

A pilot project begun in 1954 and continued for three years has shown that in a country such as Korea the treatment of pulmonary tuberculosis by attendance at clinics and home visits by a nurse, especially if accompanied by relief measures, can be successful with the majority of sufferers from this disease, and, if carried out on a large enough scale, could in a few years materially decrease its incidence. Patients in both city and country come so readily for treatment that it is difficult to cope with the increase in numbers. The patients whose condition deteriorates during treatment make up 5%, not greater than in sanatoriums in the United States. It should be noted that this report concerns only the work supported by Church World Service and does not deal with the excellent program carried on by the government of Korea through clinics in many cities.

Summary

Of those who attended chest clinics for a chest x-ray, approximately 25% showed radiologic changes consistent with a diagnosis of active pulmonary tuberculosis. In 67% of 162 patients whose sputum was positive at the beginning of treatment, sputum culture showed no evidence of tubercle bacilli at the end of one year. Eighty per cent of 162 patients showed radiologic improvement in one year; in 45% this improvement was marked. In a country clinic, in which some of 161 patients had been treated for only 8 months, 65% showed radiologic improvement.

The chief factor in the high incidence of tuberculosis in Korea appears to be the overcrowding, with all members of the family, including the patient with "open" tuberculosis, sleeping in one room, and this room often quite small. Most of the

patients attending the clinics were found to be extremely poor. A home visiting program by nurses trained for this work is considered essential for the education of the patient and the family. A relief program for poor patients helps greatly in meeting the needs of the patient.

United Church of Canada, Board of Overseas Missions, 299 Queen St. W., Toronto 2 B.

The help of a loyal Korean staff, the Korean government, the superintendents of hospitals where clinics were established, and the many donors to the Church World Service is hereby acknowledged. The largest single gift was given by Mr. and Mrs. John Hay Whitney.

CLINICAL NOTES

TREATMENT OF ANTICHOLINESTERASE INTOXICATION WITH OXIMES

USE IN NORMAL SUBJECTS AND IN PATIENTS WITH MYASTHENIA GRAVIS

David Grob, M.D.
and
Richard J. Johns, M.D., Baltimore

Intoxication by anticholinesterase compounds may occur in normal subjects after accidental exposure to organophosphorus insecticides (e. g., parathion [1] and tetraethylpyrophosphate [TEPP] [2]) and chemical warfare agents (e. g., sarin, one of the "nerve gases," isopropyl methyl phosphonofluoridate [3]). Similar intoxication may occur as a result of overtreatment of patients with myasthenia gravis with anticholinesterase medication, whether organophosphorus (TEPP or octamethyl pyrophosphoramide [OMPA]) or quaternary ammonium (neostigmine [Prostigmin], bis-neostigmine [BC-40], pyridostigmine [Mestinon], bis-pyridostigmine [hexamarium, BC-51], or ambenomium [Mytelase]).[4] These compounds inhibit cholinesterase enzymes throughout the body, resulting in local accumulation of acetylcholine, which produces increased activity of smooth muscle and secretory glands (manifested by nausea, vomiting, diarrhea, sweating, and increased salivary and bronchial secretion), bradycardia, central nervous system symptoms, muscular weakness, and fasciculations in normal subjects,[5] and increased strength which may be followed by weakness in patients with myasthenia gravis.[4a] In the management of the latter disease, graded doses of anticholinesterase compound are administered until a maximal level of strength is attained in the affected muscles. Unfortunately, in patients with severe myasthenia, the maximal strength attained may be far below normal. Increasing doses may result in no further increase in strength, and excessive use may produce generalized weakness which is accompanied by less muscular fasciculation and gastrointestinal symptoms than in normal subjects.

The administration of large doses of atropine ameliorates the gastrointestinal symptoms, sweating, salivation, bradycardia, and central neural effects produced by anticholinesterase compounds, but has no influence on the muscular weakness. In severe anticholinesterase intoxication, death occurs as a result of paralysis of the muscles of respiration and of the pharynx and tongue unless artificial respiration and an open airway are maintained until spontaneous recovery occurs.[3]

Recently, it has been demonstrated that cholinesterase inhibition, neuromuscular block, and lethal effects produced by organophosphorus anticholinesterase compounds in experimental animals may be reversed by a number of oximes.[6] This communication will present evidence that the oximes, pyridine-2-aldoxime (2-PAM) and diacetyl monoxime (DAM), are capable of reversing in man cholinesterase inhibition and neuromuscular block due to organophosphorus or quaternary ammonium anticholinesterase compounds, and are of clinical value in the treatment of intoxication by these compounds in normal subjects and patients with myasthenia gravis.

Procedure

After studies carried out in vitro [6] had demonstrated that 2-PAM and DAM protected against the inhibition of human cholinesterase enzymes by both organophosphorus and quaternary ammonium anticholinesterase compounds, and that 2-PAM reversed this inhibition, the effect of the oximes on alterations in neuromuscular function produced by these anticholinesterase compounds in normal subjects and myasthenic patients was determined. The following anticholinesterase compounds were administered intra-arterially into the brachial artery and orally: neostigmine, bis-neostigmine, pyridostigmine, bis-pyridostigmine, ambenomium, and sarin. Octamethyl pyrophosphoramide was administered orally only. After the development of alterations in neuromuscular function and strength in the

From the Department of Medicine, Johns Hopkins University and Hospital. Dr. Johns is a Kenny Foundation Scholar.

injected arm or generally, 2-PAM or DAM was administered intra-arterially or intravenously. Muscle function was determined by percutaneous electric stimulation of the ulnar nerve and by recording the evoked muscle action potentials [7] and tension. Muscle strength was also evaluated by measurement of grip strength, and of the length of time the head or each extended leg could be elevated from the

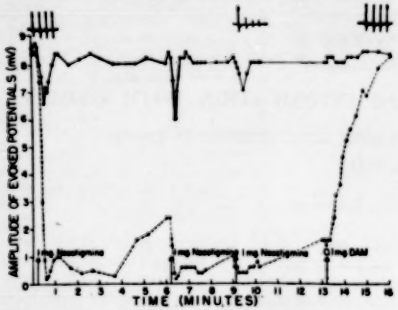

Fig. 1.—Reversal by DAM of depressant effect of neostigmine on evoked muscle action potentials and tension of normal subject. Amplitude of first (solid line) and fourth (broken line) potentials in response to train of four nerve stimuli (40 msec. apart) evoked every five seconds has been plotted, and illustrative potentials recorded above. Injections were intra-arterial.

supine position, and the arms from the sitting position. Plasma and red blood cell cholinesterase activity was determined electrometrically [8] on blood drawn from the uninjected extremity.

Results

Normal Subjects.—The intra-arterial injection of 0.05 to 0.1 mg. of 2-PAM or DAM promptly and strikingly reversed in normal subjects the local neuromuscular block produced by each of the anticholinesterase compounds studied (fig. 1). The evoked muscle action potentials and tension, which had been depressed by the anticholinesterase compounds, were restored to their initial amplitude. The prior injection of oxime protected against the neuromuscular blocking action of these compounds.

The intravenous injection of 500 to 2,000 mg. of 2-PAM or DAM over a period of 5 to 10 minutes ameliorated to a moderate degree the generalized weakness produced by the oral or parenteral administration of each of the anticholinesterase compounds studied. Muscular fasciculations were reduced to a lesser degree; occasionally they were unchanged. The improvement began within 30 seconds after injection, and was maximal in 5 to 10 minutes. Approximately 20 minutes later, there was usually some return of weakness and fasciculations but not to the original level. Another injection of oxime then resulted in further improvement. The more severe the weakness, the less striking was the improvement. In no instance was there a dramatic increase in strength comparable to the reversal of neuromuscular block observed locally after the intra-arterial injection of much smaller doses of oxime. Both 2-PAM and DAM were equally effective, and the action of each of the anticholinesterase compounds was reversed to the same degree.

Myasthenic Patients.—Prior to the administration of anticholinesterase medicaments, myasthenic patients had generalized weakness and defective neuromuscular transmission, indicated by progressive decline in the amplitude of successive evoked muscle-action potentials (fig. 2). After the administration of sufficient anticholinesterase compound to improve strength and neuromuscular transmission, the intra-arterial or intravenous injection of 2-PAM or DAM reversed this effect, resulting in return toward the original state of weakness (fig. 2).

After the administration of an excess of anticholinesterase compound sufficient to decrease strength and neuromuscular transmission, the injection of 2-PAM or DAM reversed this effect, resulting in an increase in strength (fig. 3) and in the amplitude of evoked potentials. The doses of oxime that were required and the degree of change were similar to those in normal subjects. However, whereas in normal subjects the further administration of the same doses of oxime after recovery from the effects of the anticholinesterase compound produced no change, in myasthenic patients this resulted in depression of strength and neuromuscular transmission toward the level that had existed prior to the administration of any anticholinesterase compound. As in normal subjects, 2-PAM and DAM were

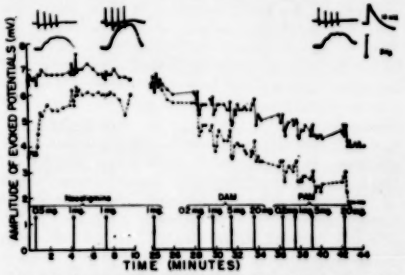

Fig. 2.—Reversal by DAM and 2-PAM of reparative effect of neostigmine on evoked muscle action potentials and tension of myasthenic patient. Amplitude of first (solid line) and fourth (broken line) potentials in response to train of four nerve stimuli (40 msec. apart) evoked every five seconds has been plotted, and illustrative potentials (mV.) and tension (kg.) recorded above. Injections were intra-arterial.

equally effective, and the action of each of the anticholinesterase compounds was influenced to the same degree.

Other Effects of Oximes

The intravenous administration of 100 to 1,000 mg. of 2-PAM or DAM usually produced slight to moderate reversal of plasma and red blood cell cholinesterase inhibition but had no effect on the gastrointestinal symptoms, sweating, salivation, bradycardia, or central neural symptoms produced by the anticholinesterase compounds. The injection of DAM at a rate of 60 to 300 mg. per minute resulted in a burning sensation radiating up the injected vein, followed by moderate giddiness, drowsiness, sensation of warmth and tingling in the abdomen and chest, and usually slight reduction in blood pressure and increase in cardiac rate, recumbent and standing. These effects lasted for one to five minutes after cessation of the injection. Injection of DAM at a slower rate, or of 2-PAM at a rate up to 300 mg. per minute, resulted in no local or systemic signs or symptoms except for slight tachycardia on standing. The intra-arterial injection of 20 mg. or more of 2-PAM, in the absence of anticholinesterase compound, produced transient weakness and neuromuscular block.[6] DAM had no such effect. Neither compound produced weakness after intravenous injection of 2,000 mg.

Report of a Case

A 60-year-old male had moderately severe generalized myasthenia gravis of three years' duration. His condition had been satisfactorily regulated with 240 mg. of pyridostigmine four times a day. He was inadvertently administered 180 mg. of enteric-coated neostigmine (long-acting) in place of his early morning dose of pyridostigmine. One hour later he developed severe nausea, abdominal cramps, explosive diarrhea, salivation, sweating, and generalized muscular fasciculations. Prior to the administration of neostigmine he had been moderately weak, at his usual basal strength. One hour after the neostigmine he became much weaker, with increased dysarthria, dysphagia, and weakness of the muscles of the face, neck, and extremities (fig. 3). His symptoms were unchanged during the next two hours. He was then given 1,000 mg. of 2-PAM intravenously over a period of 10 minutes. By the end of the period of injection there was a moderate improvement in strength and slight diminution of fasciculations. There was no change in the gastrointestinal symptoms, so that 1 mg. of atropine sulfate was then injected intravenously, with prompt amelioration of these symptoms. Fifteen minutes after the administration of 2-PAM there was a moderate decline in strength but not to the level that had been present prior to the injection of oxime. One hour later the strength again began to improve, reached the maximal level that was usually present after optimal doses of anticholinesterase medicament, and remained at this level for the rest of the day. Fasciculations gradually disappeared. There was no apparent effect of 2-PAM on plasma and red blood cell cholinesterase activity, which had been markedly depressed and which slowly returned to normal over a period of 24 hours.

Comment

The management of intoxication due to anticholinesterase compounds has hitherto relied upon administration of large doses of atropine, aspiration of bronchial and salivary secretions, maintenance of an adequate airway, and artificial respiration when needed.[3] In contrast to atropine, 2-PAM or DAM administered intravenously in adequate doses ameliorates muscular weakness and should diminish the necessity for, or duration of, mechanical measures to sustain respiration. However, since weakness may develop rapidly in the course of severe anticholinesterase intoxication, these measures will undoubtedly still be needed in many patients. The intravenous administration of adequate doses of atropine also remains an important adjunct in treatment, since the oximes do not appear to reverse the muscarine-like and central neural manifestations of anticholinesterase intoxication.

While the optimal and toxic doses of oxime and the optimal frequency of administration are not yet known, the doses employed in this study were well tolerated and moderately effective. The following procedure is therefore recommended for the management of intoxication due to organophosphorus or quaternary ammonium anticholinesterase compounds occurring in normal subjects or in patients with myasthenia gravis:

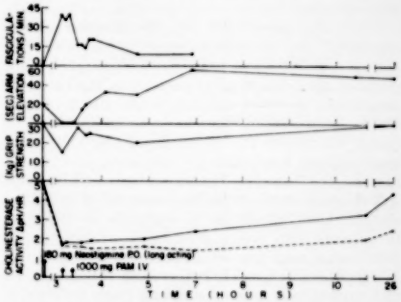

Fig. 3.—Reversal by 2-PAM of generalized weakness and muscular fasciculations produced by excess neostigmine in myasthenic patient. There was no apparent reversal of plasma (solid line) and red blood cell (broken line) cholinesterase inhibition.

1. Terminate the exposure by removal of the casualty or use of gas mask if atmosphere is contaminated by organophosphorus compound, removal of contaminated clothing, washing of contaminated skin or eyes with copious amounts of water, gastric lavage if ingestion has occurred, and application of a tourniquet if exposure is percutaneous or intramuscular.

2. Remove secretions and maintain patent airway by having patient in prone position with head down and to one side, mandible elevated, and tongue pulled forward, clear mouth and pharynx with finger or suction, maintain oropharyngeal or nasopharyngeal airway in unconscious or flaccid patients, or perform endotracheal intubation if airway obstruction persists.

3. Apply artificial respiration when necessary by mouth-to-mouth, mask-to-mask, bellows, or mechanical means.[3]

4. Administer atropine in severe intoxication, particularly by organophosphorus compounds, 2 to 4 mg. intravenously, followed by 2 mg. every three to eight minutes until muscarine-like symptoms disappear and whenever they reappear; a total of 24 to 48 mg. may be required the first day. In less severe intoxication give 2 mg. intravenously or intramuscularly, repeat at 20-minute intervals until muscarine-like symptoms are relieved; maintain a mild degree of atropinization for 24 to 48 hours.[3]

5. For oxime administration in severe intoxication, give 2,000 mg. of 2-PAM (500 mg. per minute) or DAM (200 mg. per minute) intravenously; repeat dose if weakness is not relieved, or recurs. In moderate intoxication give 1,000 mg. intravenously and repeat if weakness is not relieved or recurs.

6. Alleviate convulsions if these interfere with respiration with trimethadione (Tridione), 1 Gm. intravenously every 15 minutes up to a maximum of 5 Gm., or with sodium thiopental (2.5% solution) intravenously.[3]

While the oximes are equally effective in the treatment of anticholinesterase intoxication in normal subjects and myasthenic patients, more cautious administration is necessary in the latter. In myasthenic patients who are weak due to excess anticholinesterase medication, appropriate doses of oxime will reduce the anticholinesterase effect to a more optimal level, thereby producing an increase in strength. However, further oxime administration will decrease the anticholinesterase effect to a suboptimal level, producing a reduction in strength. In patients with severe myasthenia, overtreatment with oxime may convert a "cholinergic crisis" into a "myasthenic crisis." It is therefore recommended that myasthenic patients suffering from anticholinesterase intoxication be "titrated" with successive 500 mg. doses of 2-PAM or DAM at 5-to-10-minute intervals until strength is restored to the maximal level attained after the administration of optimal doses of anticholinesterase compound. In patients with severe myasthenia who are receiving large amounts of anticholinesterase medication, it is sometimes difficult to determine whether an increase in weakness is due to an overdose of medication (cholinergic crisis) or to the need for more drug (myasthenic crisis). The effect of oxime administration is helpful in making this differentiation: an increase in strength points to the former, and a decrease to the latter.

Summary

Intravenous administration of 1,000 to 2,000 mg. of pyridine-2-aldoxime (2-PAM) or diacetyl monoxime (DAM) ameliorated generalized weakness produced by quaternary ammonium or organophosphorus anticholinesterase compounds in normal subjects and in patients with myasthenia gravis. These oximes are valuable adjuncts to atropine in the management of anticholinesterase intoxication, and should diminish the necessity for, or duration of, artificial respiration and endotracheal intubation. More cautious administration is necessary in myasthenic patients in whom overtreatment with oxime returns strength to the basal level present prior to the administration of anticholinesterase compound.

601 N. Broadway (5) (Dr. Grob).

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The 2-PAM and DAM used in this study were supplied by Dr. Henry J. Wills of the Army Chemical Corps.

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VITAMIN A DEFICIENCY IN AN INFANT

Israel J. Wolf, M.D., Paterson, N. J.

This report presents another case of vitamin A deficiency in an infant treated for eczema with a formula of soybean milk without vitamin A supplement (Mull-Soy). The Vitamin A deficiency developed by the third month of life, probably because of low prenatal stores of Vitamin A. The mother was on a low-animal-fat diet without Vitamin A in her diet during pregnancy.

It has been stated that the common use of multiple vitamins in infancy is unnecessary, that vitamin A is abundant in milk, and that only vitamin D should be added to the infant's diet. This does not apply to infants who are allergic to animal milks and have been placed on soybean milk substitutes without vitamin A. The purpose of this report is to reemphasize the necessity for vitamin A supplementation for infants on soybean milk formulas and for rigorous supervision in this respect.

Report of a Case

History and Initial Treatment.—An infant was first seen at the age of 7 weeks with coryza and diarrheal bowel movements. He weighed 3,100 Gm. (6.5 lb.) and showed a mild eczema of the face for which he had been placed on a soybean milk formula without any vitamin supplement. He was born prematurely, weighing 1,800 Gm. (4.2 lb.). There were three other siblings and no miscarriages or deaths. One older sibling had been seen at one year of age with active rickets. The mother and sister had had asthma. The infant was kept on soybean milk formula, and the mother was instructed to give him 0.6 cc. daily of a vitamin compound containing 5,000 units of vitamin A, 1,000 units vitamin D, and 50 mg. of ascorbic acid (Tri-Vi-Sol).

He did not return for observation until two months later when he was 3½ months old and weighed only 3,400 Gm. (7.5 lb.). He had a coarse bronchitis and was anorectic. The mother had noted a facial palsy on the left. Both corneas were cloudy, and there was a catarrhal otitis media on the left. The eyegrounds could not be visualized. The mother had had a negative blood Wassermann test during her pregnancy. A blood Wassermann test on the infant proved negative, but he was treated with intramuscularly and orally given penicillin for one week without improvement.

Although the mother was advised to return with the infant within a few days, he was not seen again for almost two months. He was now 5 months old and weighed only 3,600 Gm. (8 lb.). He was still on a soybean milk formula. He had a croupy cough and a bilateral catarrhal otitis media. Both eyes were severely involved with keratitis. There was no eczema, and the skin was not dry. A facial palsy was present on the left. The neck was somewhat stiff, and the anterior fontanel was tense. The abdomen was distended. There was no gynecomastia.

On questioning the mother, she admitted that she had been erratic in giving the infant his vitamin supplement. During her pregnancy she had abhorred milk and butter. Blood was drawn from the infant for vitamin A determination, and he was given 2 cc. of an aqueous solution injectable intramuscularly, containing 10,000 U.S.P. units of vitamin A, 1,000 units of vitamin D, and vitamins E, C, and B complex (Vi-Syneral).

Attending Pediatrician, Barnert Memorial Hospital.

Hospital Course.—The infant was admitted to the Barnert Memorial Hospital on Dec. 21, 1955, for further study.

Results of Eye Consultation: An eye consultation (with Dr. Philip Opper) resulted in the following information. In the right eye there was a severe keratitis present, with a grayish look to the entire cornea. There were many phlyctenules present, and one in particular at 4 o'clock was deep and appeared ready to rupture. The pupil was small. The conjunctiva close to the limbus was dry and injected. In the left eye the cornea was more gray and opaque than in the right. There was a forward bulging of the cornea (ectasia and staphyloma) with involvement of the iris. The anterior chamber could not be visualized. The conjunctiva was dry and injected. Atropine sulfate solution, 0.5%, and a hydrocortisone (Neo-Cortef) ointment into each eye three times a day was ordered.

Laboratory Data: Urinalysis showed no sugar or albumin present. There were one to two red blood cells per high-power field and four to six leukocytes per high-power field. Amorphous urates were present. The hemoglobin level was 8.0 Gm. per 100 cc. The red blood cell count was 3,700,000 per cubic millimeter; (color index 0.74); The white blood cell count was 8,200 with 2% neutrophil stab cells, 15% polymorphnuclear cells, 78% lymphocytes, and 5% monocytes. There was moderate achromia and anisocytosis.

The blood calcium level was 12.5 mg. per 100 cc., and the blood phosphorus level was 4.4 mg. per 100 cc. A stool specimen showed no starch granules microscopically but a normal amount of fat globules. A gelatin film test showed no trypsin present in dilutions of 1:5 and 1:100. Blood Mazzini tests were negative for mother and patient. A tuberculin patch test was negative.

Serum Vitamin A and Serum Carotene Determinations: Serum vitamin A and carotene determinations were made on Dec. 21, 1955 (Dr. David Adlersberg, Mount Sinai Hospital, New York). The serum vitamin A level was zero (normal 60 to 100) mcg. per 100 cc. The serum carotene level was 26 mcg. per 100 cc. (normal 100-200).

Roentgenograms and Therapy: Roentgenograms of the heart, lungs, and long bones were normal. The skull showed widening of the suture lines. A spinal tap was attempted, but the infant became cyanotic and the procedure was discontinued.

The infant remained in the hospital for one week, during which time he received 5,000 units of vitamin A daily, the routine prophylactic dose. He was noted to have a blocked nose with a greenish nasal discharge. His neck and back were arched and he preferred to lie on his back. He was released for office care on Dec. 28, 1955.

Subsequent Course.—Although the infant received only one inoculation of aqueous vitamin A intramuscularly prior to his hospital admission and 5,000 units daily orally for seven days during his hospital stay, he showed a dramatic response to that short period of therapy. His appetite improved, he looked about him, and the cornea of the right eye began to show enough clearing so that the iris was visible. The conjunctivas were less dry. In the two weeks that followed he received a total of 50,000 units of vitamin A aqueous by injection and 262,500 units orally (18,700 units daily). At the end of the two weeks he weighed 4,500 Gm. (10 lb.). The cornea of the right eye had cleared, and a scar was visible at 4 o'clock. The left cornea still looked gray and cooked with bulging, but the phlyctenules were healing.

In April, 1956, the patient, aged 9 months, was examined. The right eye was well healed with a scar as noted. The left cornea was scarred diffusely, and the sight was im-

paired. Blood samples from the mother and baby for vitamin A determination were hemolyzed in delivery to the laboratory. On May 25, 1956, blood was drawn again from mother and patient. In the infant the serum vitamin A concentration was 43 mcg. and the serum carotene level 42 mcg. per 100 cc. In the mother the serum vitamin A concentration was 39 mcg. and the serum carotene concentration 72 mcg. per 100 cc.

In August, 1956, the patient, aged 13 months, had been able to sit up for two weeks, was taking homogenized milk, and was getting 18,700 units of vitamin A daily. Vision in the right eye was good. The iris of the left eye was not visible. In October, 1956, the patient, aged 15 months, weighed 11.8 kg. (26 lb.). He had eight teeth, but was not walking.

Comment

Although numerous cases of hypervitaminosis A have been reported in recent years, vitamin A deficiency in infancy has been observed infrequently. From 1920 to 1932, eight leading children's hospitals in the United States and Canada reported a total of 23 cases of xerophthalmia in all their admissions.[1] In 1933 Blackfan and Walbach [2] reported a case of vitamin A deficiency in an infant. In 1952 Cornfeld and Cooke [3] and in 1955 Bass and Caplan [4] each reported another.

The following presenting signs of vitamin A deficiency in infancy have been described: xerophthalmia; cornified vaginal epithelium; mental and physical retardation; anemia resistant to treatment with iron, folic acid, and liver; erythroid suppression of bone marrow; hepatosplenomegaly; increased cerebrospinal fluid pressure; seventh cranial nerve injury, and gynecomastia. The signs of vitamin A deficiency which are referable to the eyes and epithelial structures are well known. Signs referable to the nervous system, however, such as facial palsy, neck and back stiffness, and hydrocephalus, described in more recent reports, are less well known and understood.

The mechanism of the production of the hydrocephalus, reported both in cases of hypervitaminosis A as well as in hypovitaminosis A, is not clear. The increased spinal fluid pressure is relieved by tapping and vitamin A administration. The chemistry and cytology of the fluid is normal.

The diet of the mother in relationship to vitamin A deficiency in the infant is of importance. If the diet of the pregnant mother is extremely low in vitamin A, or if she is suffering from a disorder which interferes with the absorption of this vitamin, the newborn infant may have low stores of vitamin A, or even manifestations of vitamin A deficiency, as was shown by Maxwell [5] in China.

Summary

A 3-month-old infant had vitamin A deficiency. The mother was on a low-fat diet without vitamin A supplement during pregnancy. The infant's vitamin A blood level was zero at the time of initial examination. He responded well to vitamin A therapy. One eye cleared with a small residual scar; the other eye healed with considerable scarring and loss of vision. Infants who are allergic and who are on a soybean milk diet lacking in vitamin A must be rigorously supervised to see that vitamin A is added daily to the diet.

231 E. 31st St. (4).

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MALNUTRITION AND VIRAL INFECTION.—As astute observers have noted, the old concept that famine and pestilence go hand in hand does not always prove true. This was first observed by Underwood in 1789. He stated that at times well nourished children were more susceptible to infection than were poorly nourished ones. In 1942 one of us submitted this to experimental proof, and found that under certain conditions of starvation the rabbit became more resistant to infection with vaccinia. This concept has since been fully substantiated by various investigators. . . . The general consensus respecting the obligate host-parasite relationship is that any influence inhibitory to host tissue metabolism will also be inhibitory to viral agents. Our further experiments have led us to conclude that the effect of malnutrition on the resistance of an animal is dependent upon the state of the animal's nutritional reserves at the time of the infection. A well nourished animal on a poor diet becomes at first more susceptible to viral infection, then less susceptible, and terminally more susceptible again.—D. H. Sprunt, M.D., and C. C. Flanigan, Ph.D., The Effect of Malnutrition on the Susceptibility of the Host to Viral Infection, *The Journal of Experimental Medicine*, Nov. 1, 1958.

BLOOD AND URINE LEVELS IN GLUTETHIMIDE (DORIDEN) INTOXICATION

Lawrence C. Kier, Ph.D., Richard W. Whitehead, M.D.
and
William C. White, M.D., Denver

The widespread use of the popular nonbarbiturate sedative glutethimide (Doriden) has been accompanied by occasional reports of overdoses of this drug. Four fatal cases, allegedly due to poisoning by glutethimide, were documented for the first time by both autopsy reports and toxicological analysis.[1] The authors used the colorimetric method of Sheppard and co-workers [2] to measure a metabolite of glutethimide in the urine. The attempts of McBay and Katsas [1] to apply this method to blood measurements were unsuccessful. They did find that after therapeutic doses the amount of the metabolite in human urine averaged 2.2 to 2.7 mg. per hour or 4.4 to 5.8 mg. per 100 cc. for periods of 54 to 60 hours after ingestion of glutethimide. In their four fatal cases, an average of 39.5 mg. per 100 cc. of the metabolite was found in the urine. A study of the cases presented in the report indicated that the lethal dose of glutethimide for the adult human being is from 10 to 20 Gm.

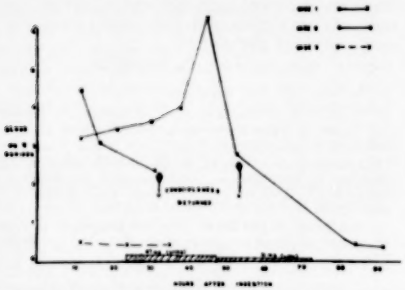

Fig. 1.—Blood glutethimide levels in three patients with glutethimide intoxication.

Report of Cases

In our experience with four nonfatal cases of glutethimide intoxication, both blood and urine levels were determined by the ultraviolet absorption method of Goldbaum and associates.[3]

Case 1 (fig. 1).—A 57-year-old female had ingested large amounts of alcohol and approximately 10 Gm. of glutethimide. Gastric lavage was not done, and the patient was given symptomatic and supportive treatment only. She remained comatose for 54 hours. The maximum blood level of 6.3 mg. per 100 cc. was not reached until 46 hours after ingestion. This was followed by a rapid decrease in the blood glutethimide level. During the 24-hour interval preceding the attainment of the maximum blood level, urinary excretion occurred at the rate of 2 mg. per hour. In the next 24-hour interval, urinary excretion occurred at the rate of 1.3 mg. per hour. The patient regained consciousness when the blood level fell below 2.8 mg. per 100 cc.

Case 2 (fig. 1).—An 18-year-old male had ingested approximately 5 Gm. of glutethimide and an unknown quantity of meprobamate. The patient was comatose upon arrival at the hospital emergency room. The maximum blood level of 4.3 mg. per 100 cc. was reached 12 hours after ingestion. The blood level then continued to fall for 32 hours, when consciousness returned. At this time the blood level was 2.4 mg. per 100 cc. The patient was discharged the next day.

Case 3 (fig. 1).—A 53-year-old female was admitted in a comatose state. It was reported that she had been drinking heavily, having consumed a fifth of whiskey in 24 hours, and that she also had taken an apparent overdose of glutethimide (amount unkown). The blood glutethimide level 12 hours after ingestion was 0.5 mg. per 100 cc., and the blood alcohol level was 163 mg. per 100 cc. The glutethimide level fell progressively until it reached a level of 0.3 mg. per 100 cc. 36 hours after ingestion. At these low blood glutethimide levels, the urinary excretion for the period from 12 to 24 hours after ingestion averaged 0.14 mg. per hour, and for the next 24 hours averaged 0.09 mg. per hour. The patient was discharged the next day.

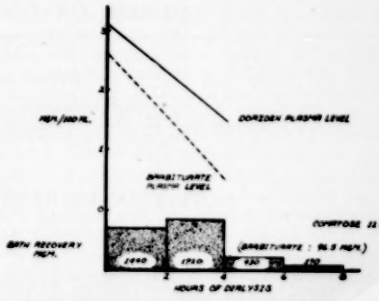

Fig. 2.—Data on hemodialysis of patient with glutethimide intoxication.

Case 4 (fig. 2).—An 18-year-old female was found unconscious after having ingested 10 Gm. of glutethimide and approximately 3 grains (0.2 Gm.) of Tuinal—a combination of

From the Division of Pathology, Denver General Hospital, and the Department of Pharmacology, University of Colorado Medical Center.

secobarbital (Seconal) sodium and amobarbital (Amytal) sodium. Gastric lavage was carried out about four hours after ingestion. The patient showed temporary improvement, which was followed by acute respiratory depression and circulatory collapse. She was then placed on therapy with the Kolff artificial kidney in an attempt to lower the drug levels by hemodialysis (see table). Blood levels immediately before dialysis (10 hours after ingestion) were 3.1 mg. per 100 cc. of glutethimide and 2.6 mg. per 100 cc. of barbiturate; four hours after dialysis they were 1.5 mg. per 100 cc. of glutethimide and 0.5 mg. per 100 cc. of barbiturate.

Analytical Results of Dialysis

2-Hr. Periods	Dialysate Levels, Mg./Hr.	
	Glutethimide	Barbiturate*
1st	720	5.6
2nd	860	7.4
3rd	215	12.5
4th	85	22.8

* Barbiturate levels were determined by ultraviolet method of Goldbaum: *Analyt. Chem.* **26**:1604 1952.

The patient was still comatose at the end of dialysis, but the respirations were deeper and the rate was 20 to 24 per minute. The patient responded to stimuli eight hours after the end of dialysis but was incoherent, restless, and cried frequently. Suction was no longer necessary. Intravenous administration of fluids was continued throughout the 24-hour period after dialysis. She continued to improve, and after another 12 hours oral feeding was started. She was emotionally disturbed throughout the day after dialysis but from that time on had a fairly normal convalescent period. She was discharged on the sixth day.

Conclusions

The ultraviolet absorption method for the analysis of glutethimide in blood and urine was used in four patients with glutethimide intoxication. The ingestion of glutethimide is followed by a fairly constant and prolonged excretion (2 to 3 mg. per hour). This result is in agreement with that of another group of workers who used a colorimetric method of analysis. The blood level of glutethimide decreases slowly after ingestion. Narcosis is produced at blood levels of 2 to 3 mg. per 100 cc. or higher. Hemodialysis removes glutethimide at a more rapid rate (100 to 400 times) than does the normal kidney. Gastric lavage should be undertaken any time after ingestion of glutethimide. Other drugs depressant to the central nervous system such as alcohol and barbiturates react synergistically with glutethimide.

4200 E. Ninth Ave. (20) (Dr. Whitehead).

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COUNCIL ON FOODS AND NUTRITION

Report to the Council

The Council has authorized publication of the following report. This article is part of a nutrition education program which is assisted by the Nutrition Foundation, Inc.

PHILIP L. WHITE, SC.D., *Secretary*

NUTRITION IN RELATION TO DERMATOLOGY

Allan L. Lorincz, M.D., Chicago

Among both lay and medical persons, there are misconceptions and fads concerning the relationship of diet and nutrition to skin eruptions. The less sophisticated tend to incriminate specific foods or "acid in the system" as causative factors, whereas the more sophisticated like to think in terms of some deficiency, especially some vitamin deficiency. Even physicians are inclined to overrate the role of food allergies or deficient diets in skin eruptions. In contrast to these beliefs, the overwhelming majority of common skin disturbances are not significantly connected with these dietary or nutritional allergies or deficiencies.

From the Section of Dermatology, Department of Medicine, University of Chicago.

Dermatological Aspects of Obesity

From the viewpoint of the present-day American clinical dermatologist, malnutrition in the form of overeating, which leads to alimentary obesity, is by far the most frequently encountered nutritional disturbance that causes or aggravates skin diseases. Obesity precipitates or promotes a variety of skin disorders in intertriginous locations, such as

nonspecific intertrigo, superficial moniliasis, pyodermas, and seborrheic and other forms of eczematous dermatitis, largely as a consequence of the accumulation of heat and moisture between folds of skin. This accumulation produces maceration of the skin in those areas and favors the growth of potentially pathogenic bacteria and fungi. Increased mechanical irritation in the form of chafing further fosters intertriginous skin disorders in the obese person. A special, rare variety of intertriginous skin disturbance associated with obesity is juvenile acanthosis nigricans, which is characterized by a melanotic, velvety verrucosity of the involved skin surfaces. The recent association with this condition of an unusual pituitary disturbance showing proliferation of anterior lobe basophils is noteworthy [1] and may offer a clue to further knowledge about factors involved in some cases in which excessive appetite results in overeating and obesity.

Because dissipation of body heat by conduction and radiation is impaired by a thick subcutaneous adipose layer, obese persons become overheated easily and, therefore, tend to sweat more profusely. The adverse effects of excessive sweating on normal skin and especially on most inflammatory dermatoses, chiefly because of sweat-retention phenomena, are well known and have been presented at length in a recent monograph.[2] So-called prickly heat or miliaria rubra is the most commonly recognized manifestation of such sweat retention.

Another large segment of dermatological ills often precipitated or aggravated by obesity consists of the common stasis eczema and ulcer syndromes. In pronounced obesity it becomes almost impossible to manage these common problems satisfactorily. Other unfavorable dermatological implications of obesity include striae distensae from excessive stretching of the skin in predisposed individuals, a frequently provocative influence on the course of psoriasis, and increased occurrence of diabetes mellitus, with its attendant cutaneous complications, such as severe pyogenic and monilial infections, diabetic gangrene, necrobiosis lipoidica diabeticorum, and hyperlipemic eruptive xanthomas. In view of the high incidence of overeating and obesity in the United States (an estimated 15 million of our population exceed their so-called ideal weights by 20%), it is not surprising that measures aimed at controlling this nutritional problem are frequently necessary in the management of skin disorders.

Dietary Restrictions

More specific restriction or modification of food intake that has practical value in dermatological therapy includes the sharp restriction of carbohydrate consumption in chronic furunculosis and hidradenitis. These staphylococcic follicular pyodermas are difficult to manage because of the ready emergence of antibiotic-resistant strains of staphylococci, the impracticability of continuous antibiotic therapy, and the failure of antibiotics to reach foci of activity often isolated by scarring. The reasons for the empirical value of low-carbohydrate intake in these infections are not definitely known. Possibly lowering of the glucose content of the skin occurs, making the skin a less favorable substrate for the causative organisms. An unconfirmed suggestion has been made that in some individuals a condition called "skin diabetes" may exist, which is characterized by excessive retention of glucose only in the skin.[3]

Most observers feel that diets excessively high in carbohydrate and fat content have a provocative effect on acne vulgaris. Experimentally, this general impression receives support from the apparently increased sebaceous gland activity that has been demonstrated in persons on such diets.[4] Although increased activity of the sebaceous glands is clearly not the only factor involved in causing acne vulgaris, it is, nevertheless, a constant feature of the disease. In general, the role of dietary factors in acne vulgaris is a minor one upon which too much popular emphasis has been placed. This view is supported by the commonly observed failure of often self-imposed rigid dietary restrictions in unhappy teen-age acne sufferers to result in anything except frustration and undernourishment.

Another dermatologically useful type of dietary restriction is the diet extremely low in fat (less than 25 Gm. of fat daily), which is of value in xanthomatoses, especially the hyperlipemic types. These diets are difficult to prepare and tend to have borderline palatability. It seems difficult to understand the reported beneficial effects that these extremely low-fat diets have on the cutaneous xanthomas seen in hypercholesterolemic xanthomatosis,[5] in view of the well-known endogenous production of cholesterol. The hypothesis has been offered that the low fatty acid content of these diets interferes with the normal intestinal resorption of cholesterol excreted into the intestinal tract by way of the biliary system. In this way, endogenously produced cholesterol could be excreted and lost from the body in fairly large quantities.

Although many attempts have been made to treat psoriasis with lipotropic agents and dietary measures, such approaches, at best, have had sporadic success. As yet, no disturbances of cholesterol or lipid metabolism have been clearly demonstrated in psoriasis. The role of specific dietary exclusions in controlling cutaneous manifestations of specific food allergies is beyond the scope of this discussion. Specific food allergies play only a very limited role in causing skin diseases, and when they do, they usually produce urticarial eruptions.

Nutritional Deficiencies

It is clear from experimental observations in man and animals that severe cutaneous disorders appear early and conspicuously in many syndromes of nutritional deficiency.[6] With the possible exception of severe pellagra, these skin disorders, however, are rarely so distinctive as to permit the diagnosis of specific nutritional deficiencies. The general lack of specificity of these cutaneous disorders is not surprising. Clinical experience teaches that pathological responses of the skin to widely varying stimuli may be identical. Moreover, intricate interrelationships among nutritional factors are such that lack of single factors often causes disturbances in the utilization or roles of other factors. From a practical clinical viewpoint, isolated deficiencies of specific nutritional factors are encountered much less frequently than are multiple deficiencies.

In general undernutrition, as occurs in genuine starvation or severe gastrointestinal diseases, the skin shows vascular pallor, dryness, and reduced elasticity. In addition, melanosis, scaling, hemorrhagic phenomena, and increased susceptibility to many sorts of infections and irritations may develop. Nutritional edema, dystrophic changes in the nails and hair, and loss of hair pigment also occur. In general, a gamut of cutaneous manifestations, classically ascribed to various specific dietary deficiency syndromes, is present in general undernutrition. Undernutrition can result through several possible mechanisms: (1) lack of intake; (2) faulty absorption; (3) faulty utilization, as illustrated by the specific inhibition of utilization of certain nutrients by antimetabolites; (4) excessive excretion; and (5) increased requirements.

Dermatological Significance of Nutritional Factors

Protein.—Deficiency of adequate protein or even improper balance of the essential amino acids in nutrition, if sufficiently prolonged, leads to negative nitrogen balance. A drop in plasma albumin then occurs before other more serious manifestations become evident. If this decrease in plasma albumin falls below about 2.5 Gm. per 100 cc., edema is likely to develop, becoming apparent first in the skin. Accompanying such edema is a striking reduction in resistance to infections, which has been partially related to inadequate ability to form antibodies. Aside from these, there are few cutaneous effects of amino acid deficiencies in man. They can be enumerated as follows: (1) the faulty growth and hypopigmentation of hair and ill-defined nutritional dermatoses found in kwashiorkor, the widespread nutritional syndrome based chiefly on protein deficiency, which occurs in weanlings and children of primitive tropical populations; (2) the pellagra syndrome based upon faulty tryptophan-nicotinic acid nutrition; and (3) the eczematous skin eruptions and deficient melanin formation observed in phenylpyruvic oligophrenia. The skin manifestations in the latter metabolic disorder, which is characterized by failure of synthesis of tyrosine from phenylalanine, have been reversed by dietary phenylalanine restriction and by tyrosine supplementation.[7] Although the mechanisms causing hair changes in kwashiorkor are the basis for much speculation, they have not yet been clarified.

The current, widely held belief, supported by the clinical impressions of a few observers, that gelatin supplementation of the diet is beneficial for brittle nails and for other nail dystrophies still requires support from critical study. It may well have the same significance as the antiquated beliefs that ingestion of calcium, vitamin A, or hair hydrolysates are of value in these little understood nail disorders.

Methionine supplementation of infant formulas is being promoted as a valuable factor in eliminating diaper rash caused by ammonia liberated from urinary urea through the action of fecal bacteria.[8] Again, more critical studies are needed to establish this claim. Local prophylaxis and topical therapy are effective and more rational approaches to the treatment of diaper dermatitis.

Vitamin A.—From a dermatological viewpoint, vitamin A has probably received the most attention of all the vitamins in the past two decades. In earlier years, on the basis of reports from the Orient and Africa, cutaneous effects of vitamin A deficiency seemed clearly defined, at least clinically, in terms of hyperkeratosis, chiefly follicular (phrynoderma), and keratinizing squamous metaplasia of various mucosal surfaces. It has been unsettling, however, that follicular keratotic skin changes are not readily produced in man or animals by uncomplicated experimental vitamin A deficiency. Furthermore, the cutaneous effects in man of intoxication from excessive vitamin A intake mimic the classically held picture of vitamin A deficiency, especially in regard to follicular hyperkeratinization.[9] Experimentally, antikeratinizing effects of vitamin A on mucosal or embryonic epithelium are well established on the basis of tissue culture studies.[10]

Vitamin A has been tried in the treatment of a vast array of skin disorders, particularly in those diseases marked by excessive keratin formation. This is true especially if keratin formation has occurred about hair follicles, such as in keratosis pilaris, pityriasis rubra pilaris, and keratosis follicularis (Darier's disease). In none of these disorders has it been possible to show consistently any direct disturbance of vitamin A or carotene absorption or metabolism, as reflected by blood levels of these substances or by ophthalmological manifestations. Huge doses of vitamin A (100,000 to 500,000 units daily) are unquestionably of therapeutic value in numerous cases of the rare diseases pityria-

V 1
195

sis rubra pilaris and Darier's disease; however, the treatment is rarely completely curative, and many patients fail to respond to it. Because of the unphysiologically large doses required, it is presumed that in these instances vitamin A functions as a pharmacologically active drug rather than as replacement therapy. The beneficial effects claimed for large doses of vitamin A administered orally, parenterally, or topically in other skin disorders associated with hyperkeratinization, such as corns, calluses, ichthyosis, senile keratoses, seborrheic warts, leukoplakia, psoriasis, eczematous eruptions, and acne vulgaris, have not found general support.

Chiefly as a result of the unrestrained barrage of advertising aimed by vitamin promoters at the public as well as at physicians, hypervitaminosis A, although rare, is perhaps a more significant problem in American medical practice today than actual vitamin A deficiency. It is characterized by scaly, rough, itchy skin, loss of hair, painful periostitis and other skeletal disturbances, hepatosplenomegaly, irritability, anorexia, and a generally unhealthy status. The syndrome is assiduously to be avoided in infants, children, and pregnant women. Avoidance of hypervitaminosis A in pregnancy is indicated by the fact that fetal skeletal anomalies have been produced in rats by excessive administration of vitamin A during pregnancy.

Acute or subacute vitamin A poisoning, such as is likely to occur in massively overdosed infants (100,000 to 600,000 units), is characterized by vomiting, increased intracranial pressure, and severe agitation. It requires prompt recognition and withdrawal of the vitamin to prevent more serious consequences, including possible collapse and death, which have been demonstrated in experimental animals. This acute vitamin A toxicity syndrome is well known in arctic regions in the form of polar bear liver poisoning. The liver of the polar bear owes its extraordinary toxicity to its enormous vitamin A content, estimated at approximately 7,500,000 units per pound.[11]

Carotenemia from excessive dietary intake of carotene leads to a yellowish discoloration of the skin, which has only cosmetic significance. It does not represent hypervitaminosis A, even though, normally, carotene can be converted to vitamin A in the body.

Vitamin B Complex.—Studies of the B complex vitamins in liver and yeast have been among the most exciting and fruitful chapters in the field of nutrition. Not only have many specific deficiency syndromes, which often have cutaneous features, been produced experimentally in man and animals by dietary means or by antimetabolites, but also the specific biochemical roles of many of these vitamins as co-enzymes in intermediary metabolism have been uncovered.

From the viewpoint of the dermatologist, the most significant application of the knowledge of B complex vitamins has been the virtual eradication of pellagra. Formerly a common disease in the southern United States, knowledge of its cause, improved dietary standards among the impoverished, and vitamin supplementation have almost eliminated it in this country except in severe chronic alcoholics and in persons with chronic severe gastrointestinal disease.

The skin lesions of pellagra, which tend to occur symmetrically and usually at first on exposed areas, are triggered by various irritant stimuli, especially by sunlight. The mechanism of this apparent light sensitivity is unknown. Early in the disease the acute lesions are sharply outlined and bright red, resembling sunburn. Bullae with separation at the epidermal-dermal junction, crusting, and desquamation may follow, after which there is dusky, reddish-brown pigmentation. Chronic lesions appear as sharply outlined, thickened, indurated, heavily scale-covered, pigmented areas. Hyperkeratotic follicular plugging is also frequently present, especially on the face. Atrophy of the skin may follow chronic lesions that can become parchment-like and melanotic. Fiery red inflammation and edema of the tongue and oropharyngeal mucous membranes occur and may be complicated by numerous aphthae-like erosions and ulcers. The latter lesions have also been observed perianally as well as by gastroscopy in the stomach. The diagnosis of pellagra is also facilitated by concomitant manifestations in the central nervous system and gastrointestinal tract.

In the genesis of pellagra, lack of the amino acid tryptophan is almost as important as nicotinic acid deficiency, because tryptophan can be converted metabolically into nicotinic acid. The treatment of pellagra with as little as 15 mg. of nicotinic acid daily is simple, but in most cases other nutritional support, in the form of adequate protein intake as well as administration of other vitamins, is desirable. Aside from its vitamin activity, nicotinic acid occasionally may have useful dermatopharmacological effects because of its ability to cause cutaneous vasodilatation; however, therapeutic claims for nicotinic acid in countless skin disorders are more wishful than true. One exception is its beneficial effect on dermatitis herpetiformis after huge doses. It shares this effect with other drugs containing the pyridine structure.

Thiamine deficiency, which results in beriberi, is reflected in the skin only by edema. This curious lack of specific cutaneous effects of deficiency of thiamine, a vitamin with most fundamental functions in normal carbohydrate metabolism, might support the contention that carbohydrate metabolism in the skin consists chiefly of an abbreviated version of Krebs's tricarboxylic acid cycle.[12]

Riboflavin deficiency is believed to result in a syndrome characterized by cheilosis or perleche, sore magenta tongue, seborrheic dermatitis about the nose and scrotum, and vascularization of the cornea. In practice, however, these rather common nonspecific findings in the average patient are often caused by other than riboflavin deficiency. Various local irritants are frequently responsible for these changes observed clinically. Experimentally, there is evidence that pure riboflavin deficiency results chiefly in delayed healing, and that even the so-called specific stigmata of this deficiency require the triggering action of local trauma, irritation, or infection. Severe rosacea keratitis hardly ever is benefited by the administration of riboflavin.

No other members of the B complex group of vitamins play any current role in dermatological practice as replacement therapy, although experimentally interesting cutaneous changes have been associated in man and animals with specifically induced deficiencies.[13] The fairly recent suggestion that seborrheic dermatitis of the sicca type, as it occurs clinically, might represent a local metabolic defect involving vitamin B_6 and that this common dermatosis responds to such vitamin therapy either topically or systemically [14] has not found support on the basis of wider experience.

The proposed role of miscellaneous B vitamins, especially pantothenic acid, in the prevention of common graying of hair in man is now antiquated. Enormous doses of *p*-aminobenzoic acid, however, when used experimentally in the treatment of lymphoblastomas, have occasionally been associated with repigmentation of gray hair.[15]

The relatively short-lived era of the effective chemotherapeutic use of *p*-aminobenzoic acid as an antirickettsial agent deserves mention. On the other hand, the use of huge unphysiological doses of *p*-aminobenzoic acid and pantothenate preparations in a wide variety of other skin and systemic disorders has not had sufficient success to warrant such use.

With the advent of antibiotics and newer chemotherapeutic agents, such as isonicotinic acid hydrozide, some B complex deficiencies have been fostered not only by reduction of supplies of some of these vitamins produced by intestinal flora but also by specific metabolic antagonism. These effects require clinical attention and alertness to their possible occurrence.

Vitamin C.—Lack of sufficient ascorbic acid results in one of the earliest recognized specific dietary deficiency diseases, scurvy. In the skin, scurvy is manifested chiefly by purpura caused by capillary fragility. Another common cutaneous finding is follicular hyperkeratosis and melanosis not unlike that classically associated with vitamin A deficiency. In scurvy there is also defective formation of connective tissue with consequent defective wound healing. For extensive burns or wounds, the utilization and requirements of ascorbic acid may increase enormously, as judged from ascorbic acid administration and urinary excretion studies performed under these conditions.

Other Vitamins.—Capillary fragility and purpura have been associated with experimental bioflavonoid deficiency, but the flavonoids have no proved dermatological usefulness. Vitamin K deficiency produces cutaneous purpura, as a consequence of defective prothrombin synthesis rather than of capillary fragility. This deficiency is sometimes encountered as a clinical entity in the newborn infant and is observed in obstructive jaundice. Vitamin K is useful clinically in counteracting the hemorrhagic effects of bishydroxycoumarin (Dicumarol) and other coumarins. Vitamin K preparations have primary vesicant actions when applied topically to the skin in high concentrations. Vitamin E has no experimental or proved therapeutic role in relation to the skin, despite many attempts to demonstrate such roles.

Vitamin D is of interest to the dermatologist. The antirachitic effect of sunlight is based upon conversion of vitamin D precursors near the skin surface to the active vitamin that it absorbed systemically. Vitamin D in huge doses had a historically short-lived but spectacular therapeutic success in lupus vulgaris, but its use has been largely rendered obsolete by the advent of highly effective antituberculosis drugs. It might be mentioned that topical applications of many members of the B complex group, as well as of vitamin D, have permitted sufficient systemic absorption percutaneously to relieve experimental specific deficiency syndromes in animals.[16]

Fats.—Much impressive experimental work has been done on the cutaneous syndrome produced in animals by deficiency of the essential unsaturated fatty acids. Studies in man suggest that deficiency of polyunsaturated fatty acids may be related to certain skin diseases, but much more investigation is needed. The popularity of internal lard therapy for various kinds of eczematous dermatitis, particularly infantile eczema, has waned, probably because of the lack of specific value.

Minerals.—Knowledge of minerals and trace elements in nutrition in relation to dermatology is experimental and largely of academic interest, because deficiencies of these elements are not encountered clinically. A possible exception is the occurrence of spoon nails in iron deficiency anemias.

Summary

In contrast to popular beliefs, food allergies or nutritional deficiencies play only an insignificant role in the skin eruptions commonly seen in the United States. Alimentary obesity is by far the

V 1
195

most frequently encountered form of malnutrition that precipitates or aggravates skin eruptions. Intertriginous eruptions and stasis leg eczema and ulcers are especially common skin disorders promoted by obesity. Sharp restriction of carbohydrate intake is a helpful adjunct in the management of chronic follicular pyodermas, and diets low in fat are of value in xanthomatoses. Dietary factors in acne vulgaris and psoriasis are generally overrated. Even in genuine nutritional deficiency, cutaneous manifestations are rarely so distinctive as to allow from them diagnosis of the specific deficiencies. In general undernutrition, the skin may show a gamut of features seen in various specific nutritional deficiencies, such as pallor, dryness, loss of elasticity, hyperkeratosis and scaling, melanosis, purpura, edema, loss of hair pigment, dystrophic hair and nail changes, and increased susceptibility to infections and irritations. Inadequate protein nutrition is reflected in the skin chiefly by nutritional edema and decreased resistance to infections.

Vitamin A in large doses has antikeratinizing effects that have sometimes been useful in the treatment of the rare diseases pityriasis rubra pilaris and Darier's disease. Similar use of vitamin A generally has not been successful in other skin disorders associated with hyperkeratosis. Severe vitamin A excesses produce serious toxic effects and are especially to be avoided in infants, children, and pregnant women. The B vitamins are of little rational use in modern American dermatological practice, although the application of knowledge of nicotinic acid can be credited with the virtual eradication of pellagra in this country. The success of ascorbic acid in treating scurvy is similarly spectacular. Ascorbic acid requirements increase under conditions requiring the repair of extensive injuries. From a dermatological viewpoint, other nutritional factors have mostly only academic interest today; they find little practical application.

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POLIOMYELITIS AND MUMPS.—The results of recent intensive clinical and experimental studies on poliomyelitis have led to the abandonment of many of the earlier concepts. The hypothesis of axonal spread of the causative organism has practically given way to the acceptance of spread via the blood stream. The significance of physical exertion as an aetiological factor has assumed lesser proportions, and the theory of an exclusive neurotropism of the poliomyelitis virus has been displaced by the concept of pantropism. Even the view of primary pantropism of the poliomyelitis virus with the capacity to produce a special neurotropic variant . . . is hardly tenable now. Most workers . . . reject exclusive neurotropism of true poliomyelitis strains, particularly as a result of the work of Enders . . . who was able to obtain poliomyelitis virus cultures in non-neural tissues. The causative organism of poliomyelitis is, therefore, one of the viruses which may settle in various organs and may cause disease in them. In this respect it resembles the virus of mumps which may affect the parotid glands, the pancreas and the sex organs, as well as the central nervous system and the meninges.—W. Linder and U. Festge, Poliomyelitis and Mumps, *German Medical Monthly*, July, 1957.

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HOME-CARE PROGRAMS

THE OLDEST program for the organized home care of patients who would otherwise require hospital care was started in Boston 162 years ago, and it is still functioning. There has been a slow but steady increase in the number of such programs in recent years. In our aging population the number of patients with chronic illnesses is expected to rapidly increase. Hospitalization for all such patients is neither possible nor desirable, and that is the main reason for home care programs. In the simpler types of home care a visiting nurse carries out the instructions of a general practitioner. More elaborate plans provide an extension of the hospital to the home. Most of the patients are referred to the home care program not from outside the hospital but from the hospital wards. Before the patient is accepted for home care, the physician who will provide this care sees the patient and determines whether he is suitable for such treatment. Meanwhile a social worker arranges to meet an adult member of the family in the patient's home to appraise the emotional climate and adequacy of help. Home care is not advisable if both patient and family do not want it.

A home care program should be set up so that patients will not feel that it is a less adequate alternative to hospital care. The patient is seen at regular intervals by attending physicians and nurses from the hospital, and should the necessity for hospital care arise he is returned at once, without the red tape of readmission. The laboratory services of the hospital and the services of the entire consulting staff are available to the patient while at home, a feature which makes for continuity of patient care.

To be eligible, a patient must be unable to attend the outpatient clinic though not necessarily bedridden. The patients selected are chiefly elderly persons with heart disease, cancer, arthritis, multiple sclerosis, and muscular dystrophy. Home care may be desirable, however, for children because of their greater susceptibility to cross infection and the emotional trauma associated with removal from the home. Home care often shortens the patient's stay in the hospital, eliminates the necessity for frequent readmissions, and prevents the hospitalization of some patients and the custodial institutional care of others.

Home care programs have other advantages. Too often removal to a hospital destroys the last traces of a patient's independence, and this is followed by rapid deterioration in his physical and mental condition. Many patients who do poorly in the hospital make notable gains on home care. In the home it may be easier to forget one's illness; subconsciously, at least, death seems farther away when one is at home. Then, there is a marked reduction in the financial burden. The fact that members of the home care team come unsummoned in bad weather as well as good makes home care seem less a matter of course than hospital care and so the patient feels that his welfare is a matter of real concern. The shorter the preliminary period of hospitalization the easier the patient's readjustment to the home environment and the easier it is for his family to accept him. An adequate home care program can be established in almost any community, and for selected patients it is the best method of management. In the words of the poet, "Be it ever so humble, there's no place like home."

a salute to
medical school progress
MEDICAL EDUCATION
WEEK ···· April 20-26

V 1
195

ORGANIZATION SECTION

RURAL HEALTH CONFERENCE

"Rather than drive a car into a bustling metropolis for medical care [some rural folks] would rely on home remedies . . ."

"We need less people in agriculture . . ."

"The student in his years of training sees a preponderance of extremely difficult cases and develops a distorted picture of the complexity of medicine as it is practiced at the family level . . ."

"The idea of 'government' taking over his [the average farmer's] medical care is galling. Health insurance is more in keeping with his philosophy . . ."

"There is a question mark on the advisability of the medical profession using the prepared diet sheets supplied by commercial concerns . . ."

Those are a few of the thought-provoking comments made by 30 authorities in the fields of health, agriculture, economics, sociology, government, education, and safety last month at the 13th National Conference on Rural Health. As the three-day session closed March 8 for some 400 registrants, the Mississippi House of Representatives voted to commend the American Medical Association and the Mississippi State Medical Association for sponsoring the meeting in Jackson. Discussions in panels and in individual presentations centered around nutritional needs, dentistry, safety, doctor-patient relationships, physician distribution, health service costs, and changing social patterns—as these topics fit into the rural scene.

"Deeds, not words, measure the doctor before the tribunal of public opinion," Dr. Howard A. Nelson, President of the Mississippi State Medical Association, told the conference. "Medicine's prestige must be measured only in terms of worth and service. What medicine is and has been doing to make the total care concept a living reality is under no act of Congress or government bureau. . . . A lot of doctors is no more the answer to our new challenges than the idle hope that people just won't get sick. Proper distribution of our doctors is the biggest part of our answer, and facilities in which they can work is just about the rest."

Dr. F. J. L. Blasingame, general manager of the A. M. A., suggested that one way of bringing better medical care to rural people was to establish area hospitals, based on accessibility to a scattered population. He said: "Most rural people have cars and don't mind driving 30 to 40 miles for medical services. But some rural folks are frightened to death of city traffic. Rather than drive a car into a bustling metropolis for medical care they would rely on home remedies."

While calling for "monitoring closely" the status of physician distribution in this country "toward satisfying unmet needs for medical service," Dr. George E. Twente of Jackson said: "Too many cooks must eat their own porridge. We run a likely risk of deterioration in the presently high quality of medical care if we wantonly and needlessly oversupply the nation with physicians who can't realize their full service potential."

Exodus, Needs, Insurance, Diet

One of the best ways of alleviating some agricultural problems may be to help people leave farms and find other jobs, according to A. F. Wiledon, rural sociologist of the University of Wisconsin. He told the conference, "Today we need less people in agriculture in order to provide the food and fiber that this country needs. . . . Farming itself has become more and more of a business—a cold, calculating, competitive business."

Mrs. William Wilkie of Widener, Ark., chairman of the Arkansas Farm Bureau Women's Committee, described the medical care needs of three groups of rural people. The farmer, she said, wants good medical care and is willing to pay a moderate price for it; the share-cropper is more likely to have some doctor bills assumed by the farm owner; but "the marginal man is indeed a sad case. In this last group is the five to fifty acre farmer who is middle aged or past. He knows no other way of life. He has no family physician. This potential patient needs a place where he can have x-ray, cardiograph and diagnosis for which he pays a nominal fee."

Calling upon physicians to be more frank with their patients, Mrs. Wilkie said: "Knowledge is more manageable than anxiety. If the patient has questions the doctor has the answers. I am only one but there are thousands more like me who say, 'You lead the way. You initiate and control the programs and we will work with you. Let us do it for ourselves, together, so that the now open hand of government will not close around all of us.' The average farmer is known for his rugged individualism. The idea of 'government' taking over his medical care is galling. Health insurance is more in keeping with his philosophy, and I'm happy to say that more than half of all farm families have it."

Mrs. John B. Rice, president of the Illinois Health Improvement Association, told the conference that her agency has been organizing rural people and

other self-employed into groups which make them eligible for Blue Cross and Blue Shield benefits at regular group rates.

The A. M. A. Council on Rural Health, according to H. H. Alp of Chicago, should take the lead in working for better nutrition for the whole nation, not just the rural areas. Alp, who is director of market development for the American Farm Bureau Federation, also said: "There is a question mark on the advisability of the medical profession using the prepared diet sheets supplied by commercial concerns. There is a great need for more basic nutritional education in our medical schools."

Safety, Preceptorship, Setting

In a panel on safety education, Dr. H. A. Matthews of Canton, N. C., said: "Accident-prone children need medical consultation as much or more

Participants in National Conference on Rural Health in Jackson, Miss., last month. Left to right, Dr. Guy T. Vise, President-elect of the Mississippi State Medical Association; Dr. F. S. Crockett, Chairman of the A. M. A. Council on Rural Health; Dr. F. J. L. Blasingame, A. M. A. General Manager, and Dr. Howard A. Nelson, President of the Mississippi State Medical Association.

than the child who has frequent colds. The wise parent will consider accident hazards in the home quite as much as shots to prevent illness."

Dr. Robert E. Reiheld of Orrville, Ohio, told the conference about the preceptorship program in his state. Such a program tends to counteract the trend toward medical specialization by familiarizing the student with day-to-day activities of the general practitioner. Many medical students, said Dr. Reiheld, are overly exposed to a specialist environment because they attend medical schools and take residency training in metropolitan areas and encounter difficult cases in urban medical centers. "The student in his years of training sees a preponderance of extremely difficult cases and develops a distorted picture of the complexity of medicine as it is practiced at the family level," said Dr. Reiheld.

Urging that farm people evolve a sound agricultural program "with the sympathetic interest and cooperatin of other groups," and rely less and less on government, Mrs. Charles W. Sewell of Otterbein, Ind., co-founder of the A. M. A.'s rural health program, said: "In this way the income of farm communities will support living conditions that will attract well-trained young physicians into rural areas and maintain clinics and hospitals necessary to the best modern day practice of medicine."

Her stand was echoed by fellow founder F. S. Crockett of Lafayette, Ind., chairman of the A. M. A. Council on Rural Health. "Most of the things that mean so much, that contribute so much to making a house a home, or a plot of land a farm home, can be created by ourselves or with the help of neighbors," said Dr. Crockett. "We don't have to wait for somebody sent from the Governor or President's office to do it for us. . . . Health is influenced by much more than just good medical care. I have in mind good schools and churches, hard-top roads to market, efficient telephone and power services, a good county health service, an effective county agent promoting improved farm management and production practices, and county home demonstration agents interesting the home makers in more attractive living."

Other members of the Council are Drs. W. J. Weese of Ontario, Ore.; W. A. Wright of Williston, N. D.; W. W. Washburn of Boiling Springs, N. C.; C. S. Mundy of Toledo, Ohio; C. R. Henry of Little Rock, Ark.; F. A. Humphrey of Fort Collins, Colo.; N. H. Gardner of East Hampton, Conn.; A. T. Stewart of Lubbock, Texas; and C. B. Andrews of Sonoma, Calif.

SEMINAR ON MEDICAL WRITING FOR REPORTERS

The A. M. A. and the National Association of Science Writers are jointly sponsoring a series of seminars or workshops in medical writing for newspaper reporters. The first conference will be held at the Hotel Syracuse, Syracuse, N. Y., on Thursday and Friday, April 17-18.

Invitations are being mailed to editors of daily newspapers within a 300-mile radius of Syracuse, asking them to send one of their reporters to the meeting. County medical societies in the same area are invited to send a public relations representative.

The purpose of the conferences, which will be held in various sections of the country, is to reach those newspaper writers who work on medical assignments but also handle other duties.

The role of the A. M. A. in the joint conferences was approved by the Board of Trustees some time ago. The National Association of Science Writers, made up of newspaper and magazine reporters who specialize in medical and scientific subjects, has given its wholehearted cooperation to the project.

V 16
1958

MEDICAL NEWS

CALIFORNIA

Dr. Golden Honored.—Dr. Ross Golden, visiting professor of radiology at the University of California School of Medicine, Los Angeles, has received the Gold Medal of the American College of Radiology. Dr. Golden, until his retirement last year, was professor of radiology and chief of the department, Columbia University College of Physicians and Surgeons, New York City. In the college's nearly 40-year history, only 18 others have been presented the Gold Medal honor.

Personal.—Dr. Mark Lewis Gerstle Jr. has been appointed psychiatrist in chief-director of special treatment program to the "Youth Authority of the State of California." He assumed his new duties in Sacramento Jan. 27.——Dr. Charles M. Carpenter, professor of infectious diseases and chairman of the department, University of California Medical Center, Los Angeles, was recently awarded a certificate of merit by the National Society for Medical Research "in recognition of vital contributions to public health and welfare made by helping to inform the public of the experimental method underlying the achievements of biological sciences." ——Appointment of Dr. Charles E. Smith, dean, School of Public Health, University of California, and president, State Board of Public Health, to the National Advisory Allergy and Infectious Diseases Council was announced March 10 by the Surgeon General of the U. S. Public Health Service.

State Medical Meeting in Los Angeles.—The 87th annual session of the California Medical Association will be held April 27-30 at the Ambassador Hotel, Los Angeles. Dr. Frank A. MacDonald, president of the association, will present an address April 28. The general meetings include a panel discussion on congenital heart disease, moderated by Dr. Forrest H. Adams, Los Angeles; a clinical-pathological conference, moderated by Dr. Donald W. Petit, Pasadena; and a symposium, "Inflammatory Diseases of the Colon," with Dr. William K. Jennings, Santa Barbara, as chairman and including the following sub-topics:

Diverticulitis, Dr. Leon Goldman, San Francisco.
Ulcerative Colitis, Dr. Charles S. Davidson, Boston.
Micrococcic Enterocolitis, Dr. William A. Altemeier, Cincinnati.
Round-Table Discussion.

A motion picture, "Acute Atomic Radiation," will be presented by Lt. Col. Gerald M. McDonnel, M. C., U. S. Army, Washington, D. C. Guest speakers include Drs. Altemeier and Davidson and Drs. Thomas Parran, Pittsburgh; Marcus M. Ravitch, Baltimore; Bronson S. Ray, New York City; Olav E. Hallberg, Rochester, Minn.; Ernst L. Wynder, New York City; and Lt. Col. McDonnel. Scientific exhibits and motion-picture sessions are planned. The president's dinner dance will be held April 29. For information write the California Medical Association, 450 Sutter St., San Francisco 8.

IDAHO

Dr. Carver Appointed Health Administrator.—Dr. Terrell O. Carver, Boise, assumed his duties as State Health Administrator under the State Board of Health on Feb. 1. Dr. Carver fills a position that has been vacant since the new Board of Health was appointed by Governor Robert E. Smylie last year. Prior to coming to Idaho, Dr. Carver was Louisiana State Tuberculosis Control Officer. He served as director of preventive medicine, Idaho Department of Public Health, and for the past several years has been director of the City-County Health Department, Boise, and director of Health Program, Boise City Schools. In his new position, Dr. Carver will also serve as secretary to the State Board of Health and will be in charge of all public health activities in Idaho. Serving under him will be the director of public health and the director of mental health.

KENTUCKY

General Practice Meeting in Louisville.—The seventh annual scientific assembly of the Kentucky Chapter of the American Academy of General Practice will be held April 23-25 at the Brown Hotel, Louisville. Dr. William E. Becknell, president, Kentucky Chapter, and Dr. John S. Harter, vice-president, Kentucky State Medical Association, will present addresses the morning of April 23. About 20 papers are scheduled for presentation including those by the following out-of-state speakers: Drs. James A. Campbell, Chicago; Arthur C. Kerkhof, Minneapolis; John L. Reichert, Chicago; A. Aaron Mintz, Houston, Texas; John M. Howard, Birmingham, Ala.; Arthur C. Curtis, Ann Arbor, Mich.; Charles F. Geschickter, Washington, D. C.; Oscar Creech Jr., New Orleans; George L. Tully Jr., Albany, N. Y.; Richard W. Te Linde, Baltimore; and Harwell Wilson, Memphis, Tenn. Speaker at the annual banquet will be Dr. Austin Smith, editor

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

of THE JOURNAL, presenting "The Future for the General Practitioner." Exhibits and a ladies' program are scheduled. Ten hours of formal credit will be given for attendance. For information write the Kentucky Academy of General Practice, 141 W. McMillan St., Cincinnati 19.

MARYLAND

State Faculty Meeting in Baltimore.—The annual meeting of the Medical and Chirurgical Faculty of Maryland will be held April 16-18 at the Alcazar, Baltimore. An illustrated panel discussion, "Medical and Surgical Treatment of Tuberculosis," will be moderated by Dr. Edmund G. Beacham, chief, Tuberculosis Division, Baltimore City Hospitals. Dr. Lester R. Dragstedt, chairman, department of surgery, University of Chicago, will present the Ridgeway Trimble Fund Lecture, "A Concept of the Pathogenesis of Gastric and Duodenal Ulcer." Twenty-five topics are scheduled for the round-table luncheon session April 17. The Harvey Grant Beck Memorial Lecture will be given by Dr. Sara M. Jordan, director, department of gastroenterology, Lahey Clinic, Boston, April 18, to be followed by an illustrated clinical-pathological conference. Dr. John S. Eastland will present the presidential message after the presidential dinner. Dr. David B. Allman, president, A. M. A., will speak on "Medical Science: Man's True Glory" at the general meeting. For information write Dr. Everett S. Diggs, 1211 Cathedral St., Baltimore.

MASSACHUSETTS

Program for Technological Writing.—A two-week program for members of publications groups engaged in technological writing for industry and government will be presented at Tufts University in Medford during the last two weeks in July. Enrollment is limited to 25. No formal requirements are set for admission; the goal of the program is to assemble a group with varied backgrounds and common interests who will profit from two five-day weeks of intensive work in technical writing and editing. Participants will be urged to bring with them for discussion nonclassified reports, manuals, or other publications which their companies or agencies have prepared. Paul H. Flint, assistant dean of the Tufts Graduate School will direct the program, and the staff will be drawn chiefly from members of the Boston Chapter of the Society of Technical Writers and Editors. The fee is $150.

Personal.—Dr. Nicholas J. Semenza, of Waltham, received the annual brotherhood award of the Waltham Lodge, B'nai B'rith, at the annual award dinner March 23. Now serving as president of Lions International Club of Waltham, Dr. Semenza served as president of Sacred Heart Holy Name Society in Waltham in 1950-1952; associate editor of Sons of Italy Magazine; member of the executive council, Whittemore School Parent-Teacher Association; and medical director of the Stigmatine Seminary.——Dr. Jacob Furth, associate director of research, Children's Cancer Research Foundation, Boston, has received the 1958 Bertner Foundation award of the University of Texas M. D. Anderson Hospital and Tumor Institute. The award is presented annually "for an outstanding contribution to the field of cancer research." Dr. Furth also presented the Bertner Foundation Lecture, "Radiation Neoplasia and Endocrine Systems."

MICHIGAN

Regulations on Radiation.—State regulations that protect the general public and specialized workers against overexposure to ionizing radiation have been adopted by the state health commissioner, approved by the Council of Health, and made a part of the state administrative code. Dr. Albert E. Heustis, state health commissioner, said the regulations "apply to all persons who receive, possess or use materials or devices capable of emitting ionizing radiation." Industrial, dental, and medical users of radiation materials are covered by the regulations, which will be administered by the Michigan Department of Health. Under the new regulations, all sources of ionizing radiation including x-ray machines must be registered with the state health department. Owners of radiation equipment can obtain registration forms by writing to the Michigan Department of Health, Lansing 4. The new regulations prohibit the use of fluoroscopic shoe fitting machines on persons under 18 years of age. The regulations also created a nine-member radiation committee appointed last week by the state health commissioner to advise the commissioner on radiation protection.

MISSOURI

University News.—Dr. Ward Darley, executive director, Association of American Medical Colleges, Evanston, Ill., has accepted the invitation of the University of Missouri School of Medicine to give the Assembly Lecture sponsored by the School of Medicine. On April 23, 8:00 p. m., in the Auditorium of the Medical Center. Dr. Darley will talk about medical education, the physician-patient relationship, and the art of medicine.

NEW YORK

Dr. Glenn Receives Medical Faculty Award.—Joseph L. Glenn, Ph.D., assistant professor of biochemistry, Albany Medical College, has been named

V 16
1958

to receive a Lederle Medical Faculty Award. The $22,000 award will be made available to the college's department of biochemistry to support Dr. Glenn's teaching and research projects during the next three years. The Lederle grants are given to "promising" teachers and investigators in the preclinical sciences. They are made by the Lederle Laboratory Division of the American Cyanamid Company. Only one candidate from a medical school is considered for the award in any given year. Dr. Glenn served as a research associate at the Institute for Enzyme Research, Madison, Wis., until his appointment to the Albany Medical College faculty in 1956.

New Meat-Inspection Program.—The Division of Standards and Purchase has announced that it will accept contracts for meat from establishments operating under the State Health Department's new meat inspection program. This is the first time the division has recognized other than federally-inspected meat for use by the state. If the meat producers and packers are otherwise eligible, they can now substitute state inspection for federal inspection. The new program, as outlined in Chapter 18 of the Sanitary Code, went into effect Dec. 16. The regulation sets standards for local meat inspection programs and covers meat not federally inspected. The program provides that all slaughterhouses in health districts conforming to the code must have facilities for the inspection of animals both before and after slaughter. Among the provisions of the regulation are those dealing with sanitation, lighting, ventilation, water supply, sewage, refrigeration, protection of meat against contamination, and removal of refuse.

New York City

Doctors' Benefit Concert.—The Doctors' Orchestral Society of New York will present a benefit concert for the National Cystic Fibrosis Research Foundation on May 22. Physicians, dentists, and members of allied professions are invited to become members. For information write Dr. Benjamin A. Rosenberg, 909 President St., Brooklyn 15, N. Y.

Radiology Training Available.—The City of New York Department of Hospitals has announced that there are several vacancies available for one year of training in radiology, with maintenance and honorarium, for anyone interested in learning radiology as an adjunct to his current specialty. For information write Dr. Henry K. Taylor, Roentgenologist, Goldwater Memorial Hospital, Welfare Island 17, N. Y.

Symposium on Basal Ganglia Surgery.—A three-day symposium on "Basal Ganglia Surgery for Involuntary Movement Disorders," sponsored by the Medical Center, St. Barnabas Hospital, the Sister Elizabeth Kenny Foundation, and its subsidiary, the American Rehabilitation Foundation, will be held at New York University–Bellevue Medical Center May 15-17. Dr. Irving S. Cooper, professor of research surgery in the department of surgery of the university Post-Graduate Medical School and director of the department of neurosurgery at St. Barnabas Hospital, is symposium chairman. Panel speakers include Dr. Traugoot Reichert, professor, Neurochirurgische Klinik der Universitat, Freiberg, Germany. For information and reservation blanks write Miss Dorothy P. Frome, Office of Public Relations, 550 First Ave., New York 16.

NORTH CAROLINA

Kafer Memorial Hospital Changes Name.—Kafer Memorial Hospital of New Bern is now known as the Eastern North Carolina Baptist Hospital. The new administrator, Mr. Parker Morton, comes from Cape Fear Memorial Hospital, Fayetteville. The hospital is a forerunner of what will eventually be a brand new 108-bed unit. As soon as $600,000 has been raised construction will start on a new four-story building. Building is scheduled for completion by 1960.

University News.—The University of North Carolina, Chapel Hill, has announced the receipt of a grant of $8,061 from the Atomic Energy Commission for the purpose of equipping a radiation laboratory in the department of sanitary engineering of the School of Public Health. The laboratory is to be used for research and for teaching graduate students enrolled in programs of study in sanitary engineering, sanitary science, and sanitary chemistry and biology. Information concerning graduate study, assistantships, and fellowships may be obtained from the Department of Sanitary Engineering, P. O. Box 899, Chapel Hill, N. C.

OHIO

Fellowship in Pediatric Renal Research.—A fellowship in renal research will be available beginning July 1 in the department of pediatrics, Western Reserve University School of Medicine. The candidate will be expected to spend about two-thirds of his time in laboratory research and one-third in clinical work with patients under investigation. Salary will be $4,500 to $5,000. Applicants with minimum training of two years in pediatrics will be preferred. Direct correspondence to Dr. Walter Heymann, 2103 Adelbert Rd., Cleveland 6.

OREGON

Gift Enlarges Medical School Campus.—Boundaries of the University of Oregon Medical School campus have been extended to include a 27-acre tract of land as a result of action taken at the January State Board of Higher Education meeting. The acreage

came as a gift from the Journal Publishing Company. This property adjoins the Sam Jackson Park tract which comprises most of the present campus of the Medical School and which represents a gift made in 1904 from the Jackson family. With the addition of this tract, the Medical School campus has been increased to 101 acres.

PENNSYLVANIA

Appoint Health Center Study Committee.—Appointment of a special study committee to consider the relationship of the various elements of the University of Pittsburgh Health Center and to recommend methods of establishing more effective liaison has been announced following a recent meeting of representatives of Children's, Elizabeth Steel Magee, Eye and Ear, Presbyterian, and Women's hospitals, Western Psychiatric Institute, the Child Guidance Center of Pittsburgh, and university officials. Named to head the committee was Dr. Thomas Parran, dean of the Graduate School of Public Health. The committee will be charged with the responsibility of designing and directing the study and will bring in a recommendation for any necessary changes in relationships or long-range plans for further development to be presented to the boards of the several institutions by June 30.

Philadelphia

Personal.—Dr. Joseph B. Wolffe, cardiologist, has been given State Department approval to attend the 12th Congress of the International Federation of Sports Medicine in Moscow May 29-June 3. Scientists planning the congress have asked Dr. Wolffe to lecture on his work dealing with the role of physical activity in the treatment and possible control of hardening of the arteries. Dr. Wolffe is founder and medical director of the Valley Forge Heart Hospital and Medical Center and of the Wolffe Clinic and Hospital.

TENNESSEE

Dr. Callison to Be Dean of Medicine.—Dr. Maston K. Callison, Memphis specialist in internal medicine, will assume the office of the dean of the University of Tennessee College of Medicine July 1, succeeding Orren W. Hyman, LL.D., who has been dean of the college since 1925. Dr. Hyman will retain his position as vice-president of the university, in charge of the Medical Units, the title he has held since 1948. Associate professor of medicine, Dr. Callison has served for several years as chief of staff of the City of Memphis Hospitals. He is a diplomate of the American Board of Internal Medicine, member of American College of Physicians, American Heart Association, American Rheumatism Association, and Memphis Academy of Internal Medicine.

Annual State Meeting in Gatlinburg.—The 123rd annual meeting of the Tennessee State Medical Association will be held April 20-23 in Gatlinburg with headquarters at the Civic Auditorium. Specialty societies will meet the afternoons of April 21-23. Two symposiums are planned: "Automobile Accidents," moderated by Dr. Harmon L. Monroe, Erwin, and "Emotional Illnesses," moderated by Dr. Joseph W. Johnson Jr., Chattanooga. A panel discussion, "Management of the Patient with Inoperable Cancer," is planned. Formal presentations at the general sessions will be followed by discussions. Guest speaker at the president's banquet April 21 will be Kenneth McFarland, Ph.D., Topeka, Kan., presenting "Ropes of Gold." A movie, exhibits, and a ladies' program are arranged. For information write the Tennessee State Medical Association, 112 Louise Ave., Nashville 5, Tenn.

WASHINGTON

Symposium on Endocrine Diseases.—The Clinical Society of the Washington Diabetes Association will present the fourth annual Symposium on Metabolic and Endocrine Diseases at the University of Washington School of Medicine, Seattle, April 19. Guest speakers include Dr. Arnold Lazarow, head, department of anatomy, University of Minnesota, Minneapolis, and Dr. Gilbert S. Gordan, associate professor of medicine, University of California, San Francisco. Registration fee is $5. For information write the Washington Diabetes Association, P. O. Box 228, Seattle 11.

WEST VIRGINIA

State Society of Internal Medicine.—The first meeting of the executive committee and council of the West Virginia Society of Internal Medicine, as a state component of the American Society of Internal Medicine, was held in Huntington March 9. District chapters are functioning at Charleston and Huntington and other chapters are planned to cover all sections of the state. The state officers are: Dr. Joseph M. Farrell, Huntington, president; Dr. Pat A. Tuckwiller, Charleston, president-elect; Dr. Rowland H. Burns, Huntington, secretary-treasurer; Council: Drs. Adam B. C. Ellison, and William A. Thornhill Jr., Charleston, and William E. Bray Jr., and Walter E. Vest, Huntington. Twenty-seven states are now organized and the remainder are undergoing organization. The objectives of the society are to study the economics of internal medicine and to educate the public as to the aims and importance of the specialty of internal medicine.

WISCONSIN

Poison Information Center.—A Poison Information Center opened at the University Hospitals at Madison on April 7. The 24-hour, year-around service is available to all Wisconsin physicians by calling the

V 1
1958

hospital, ALpine 6-6811, and asking for the Poison Information Center. The center was set up in the department of pediatrics under Dr. Nathan J. Smith, head of the department. Dr. W. Theodore Bruns, who formerly directed the poison information center of the University of California at Los Angeles, is in charge. Information regarding some 250,000 potentially poisonous substances are available partly by means of a card file supplied and kept up to date by the National Clearinghouse for Poison Control Centers, of the Federal Department of Health, Education and Welfare, and partly by means of a shelf of reference books purchased for the center by the Dane County Medical Society. Furthermore, on call from the center are special consultants in various university departments such as toxicology, pharmacology, pharmacy, biochemistry, botany, mycology, agronomy, and entymology.

ALASKA

Study of Eskimo Nutrition.—A team of food and nutrition specialists is in Alaska working on the first large-scale study of the nutritional status of Alaskan Eskimos, the Public Health Service has announced. Ten native villages will be visited by the team and about 1,000 Eskimos will participate in physical examinations and biochemical studies designed to show how well the native diet meets nutritional requirements. The study will also involve two Eskimo battalions of the Alaskan National Guard. The survey is under the supervision of the Government's Interdepartmental Committee on Nutrition for National Defense. The Public Health Service's Arctic Health Research Center is assisting in the project. The native diet has been under study for the past two years by Dr. Christine Heller, of the research center. Since January, 1956, on request of the governments concerned, similar surveys have been completed in Iran, Pakistan, Korea, the Philippines, Turkey, and Libya as part of the U. S. Mutual Assistance Program. At the request of the Spanish Government, a nutritional survey will be made in that country later this year.

GENERAL

Meeting of Neurological Surgeons.—The 49th meeting of the Society of Neurological Surgeons will be held April 18-19 at Duke University, Durham, N. C. Sixteen papers are scheduled including "Craniopharyngiomas" by Dr. Edgar A. Kahn, president of the society. Other speakers include Charles M. Pomerat, Ph.D., professor of cytology, University of Texas Medical Branch, Galveston, who will present "Recent Advances in the Study of Brain Tissue in Vitro." A movie, "Intimectomy of the Internal Carotid Artery and Carotid Bifurcation in the Neck," will be shown by Dr. Elisha S. Gurdjian. The annual dinner will be held April 18 at the Washington Duke Hotel. For information write Dr. Bronson S. Ray, Secretary, Society of Neurological Surgeons, 525 E. 68th St., New York 21.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	March 15, 1958: Paralytic Type	March 15, 1958: Total Cases Reported	March 16, 1957 Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	..	..	..
Rhode Island	..	..	..
Connecticut	..	..	..
Middle Atlantic States			
New York	..	..	..
New Jersey	..	..	..
Pennsylvania	..	..	2
East North Central States			
Ohio	..	..	..
Indiana	..	..	1
Illinois	..	..	..
Michigan	..	..	2
Wisconsin	..	..	..
West North Central States			
Minnesota	..	..	1
Iowa	..	..	..
Missouri	..	..	1
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	..	..	1
Kansas	..	..	..
South Atlantic States			
Delaware	..	..	..
Maryland	..	..	..
District of Columbia	..	..	..
Virginia	..	..	1
West Virginia	..	..	..
North Carolina	1	1	1
South Carolina	..	..	..
Georgia	..	..	2
Florida	..	..	4
East South Central States			
Kentucky	..	..	..
Tennessee	..	1	2
Alabama	..	..	..
Mississippi	..	..	..
West South Central States			
Arkansas	..	..	1
Louisiana	..	..	2
Oklahoma	..	..	..
Texas	..	1	5
Mountain States			
Montana	..	..	..
Idaho	..	..	..
Wyoming	..	..	..
Colorado	..	..	1
New Mexico	1	1	..
Arizona	..	..	..
Utah	..	..	1
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	..	..	2
California	1	1	4
Territories and Possessions			
Alaska	..	..	..
Hawaii	1	1	..
Puerto Rico	..	..	..
Total	4	6	34

Nuclear Medicine Meeting in Dallas.—The third annual meeting of the Southwestern Society of Nuclear Medicine will be held at the Baker Hotel, Dallas, April 12-13. Dr. Jack G. S. Maxfield, president of the society, will present an address April 12. Sixteen papers and the following panel discussions and moderators are scheduled:

Evaluation of Scanning in Clinical Medicine, Dr. Frederick J. Bonte, Dallas.
Responsibilities of the Physician in the Nuclear Age, Dr. James R. Maxfield Jr., Dallas.
Radioiodine-Therapeutic Problems in Thyroid Disease, Dr. Philip C. Johnson, Oklahoma City.

For information write the Southwestern Society of Nuclear Medicine, 2711 Oak Lawn Ave., Medical Center Station, Dallas 19, Texas.

Residency Traineeships in Psychiatry.—The Institute of the Pennsylvania Hospital has established special four-to-five-year traineeships in support of careers in academic psychiatry. These fellowships are designed to offer a broad and integrated training in clinical psychiatry with emphasis on basic and clinical research and research training. The program in basic sciences will be conducted in collaboration with the Institute of Neurological Sciences, School of Medicine, University of Pennsylvania, Philadelphia. Applications from graduates of A. M. A. approved medical schools are invited. The stipends will depend on the applicant's qualification and research experience, and are commensurate with postdoctoral traineeships. For information write the Director of Research, the Institute of the Pennsylvania Hospital, Philadelphia 39.

Railway Surgeons Meeting in Chicago.—The 70th annual meeting of the American Association of Railway Surgeons will be held at the Drake Hotel, Chicago, April 17-19. About 16 papers are scheduled for presentation. A panel discussion, "Anticoagulant therapy," will be moderated by Dr. John H. Olwin, clinical associate professor of surgery, University of Illinois College of Medicine, Chicago, and will include the following members of the University of Illinois faculty: Drs. Oglesby Paul, associate professor of medicine; Norman B. Roberg, associate professor of medicine; William S. Dye Jr., clinical instructor in surgery; and J. L. Koppel, Ph.D., department of surgery. A symposium on "Multiple Injuries" will be moderated by Dr. Raymond Householder, Chicago, on April 18. Movie sessions will be held the afternoon of April 19, and the annual banquet will be held April 18, 7:30 p. m. For information write Dr. Chester C. Guy, Secretary, American Association of Railway Surgeons, 5800 Stony Island Ave., Chicago 37.

a salute to
medical school progress
MEDICAL EDUCATION
WEEK · · · · April 20-26

Northeast Conference on Mental Health.—An address of welcome by Governor Averell Harriman April 24 will open the meeting of the Northeast State Governments Conference on Mental Health April 23-25 at the Henry Hudson Hotel, New York City. Delegates from 10 northeastern states will convene to discuss aspects of community mental health under the theme, "Perspectives in State Mental Health Programs." Dr. Dale C. Cameron, director of the Division of Mental Health and Medical Care, Minnesota State Department of Public Welfare, will be the principal speaker. Dr. Paul H. Hoch, New York State Commissioner of Mental Hygiene, will be the dinner speaker. The conference, organized in 1951 to consider mutual problems of community mental health, comprises the states of Connecticut, Delaware, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. Representatives of the federal Department of Health, Education, and Welfare and the Council of State Governments also participate in conference activities.

V 16
1958

Awards for University Lecturing and Research.—The 1959-1960 U. S. Government Awards authorized by Public Law 584 (The Fulbright Act), under the auspices of the Board of Foreign Scholarships and the Department of State, for university lecturing and advanced research in Latin America, South and Southeast Asia and the Pacific, and Ireland are open for application. Eligibility requirements are: U. S. citizenship, a year of college or university teaching experience (for lecturing), a doctoral degree or recognized professional standing (for research), and a knowledge of the language of the host country (in some cases). Awards are tenable in one country, usually for an academic year, and payable in currency of the host country. Round trip travel for the grantee (not for family), maintenance allowance, and a small incidental allowance are provided. Closing date for application is April 25. For application and information write the Conference Board of Associated Research Councils, Committee on International Exchange of Persons, 2101 Constitution Ave., Washington 25, D. C.

Pediatricians Meeting in New York City.—The spring session of the American Academy of Pediatrics will be held April 21-23 at the Hotel Statler, New York City. The program includes the following panel discussions and moderators:

Viral Infections Involving the Respiratory Tract, Dr. Horace L. Hodes, New York City.
Recognition and Therapeutic Implications of Heart Disease in Early Infancy, Dr. Sidney E. Blumenthal, New York City.
Aspects of the Care of Newborn and Premature Infants, Dr. Richard L. Day, New York City.
Staphylococcal Infections, Dr. Hattie E. Alexander, New York City.

A symposium, "Recent Studies in Pediatric Neurology," will be moderated by Dr. Sidney Carter, New York City, April 23. Hospital clinics will be conducted at six hospitals the afternoon of April 23. Guest speaker at the April 21 luncheon will be Mr. Bennett Cerf. Exhibits, a ladies' program, and the banquet April 22 are scheduled. For information write the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

Obstetricians Meeting in Los Angeles.—The sixth annual meeting of the American College of Obstetricians and Gynecologists will be held April 21-23 at the Hotel Statler, Los Angeles. The presidential address will be delivered by Dr. R. Gordon Douglas. The program includes the following panel discussions and moderators:

Medico-Legal Aspects of Obstetrics and Gynecology, Dr. William B. Thompson, Hollywood, Calif.
Psychosomatic Aspects of Operative Obstetrics and Gynecology, Dr. Allan C. Barnes, Cleveland.
Current Concepts of Obstetrical and Gynecological Endocrinology, Dr. Charles E. McLennan, San Francisco.
Current Trends in Medical Education, Dr. Howard C. Taylor Jr., New York City.
Pediatric Gynecologic Surgery, Dr. Thomas L. Ball, New York City.

Eight research project reports will be presented the afternoon of April 23. Motion-picture sessions, exhibits, breakfast conferences, and 40 round-table discussions are planned. Entertainment includes banquets at the Ambassador Hotel and the Moulin Rouge. Fee for nonfellows is $20. For information write the American College of Obstetricians and Gynecologists, 15 S. Clark St., Chicago 3.

Annual Meeting on Sterility.—The 14th annual meeting of the American Society for the Study of Sterility will be held April 18-20 at the Beverly-Hilton Hotel, Beverly Hills, Calif. The presidential address, "What's 'New' in Infertility—A Look Back," will be presented by Dr. Charles M. McLane, New York City, at the president's luncheon, April 19. The program includes a movie, "Ovulation and Egg-Transport in the Rat," presented by Dr. Richard J. Blandau, Seattle; "Arborization of Cervical Mucus, Nasal Mucus and Saliva," by Dr. Bernard Zondek, Jerusalem, Israel; and a panel discussion, "Endocrine Assays and Their Clinical Application to the Study of Sterility," with Dr. C. Frederic Fluhmann, San Francisco, presiding. Six clinical and laboratory demonstrations are planned at various Los Angeles institutions. The Ayerst Lecture, "Studies on the Mechanism of the Female Genital Function," will be given by Dr. Zondek April 20. Scientific and technical exhibits and breakfast round-table discussions are scheduled. Fee for nonmembers is $5. For information write Dr. Herbert H. Thomas, Secretary, American Society for the Study of Sterility, 920 S. 19th St., Birmingham, Ala.

Physicians Meeting in Atlantic City.—The 39th annual session of the American College of Physicians will be held April 28-May 2, with headquarters at the Convention Hall, Atlantic City, N. J. The president's address, "Fellowship and Citizenship," will be given by Dr. Richard A. Kern at the annual convocation, April 30. The John Phillips Memorial Lecture, "The Disease Spectrum of Human Histoplasmosis," will be given by Dr. Amos Christie, Nashville, Tenn., and the Lilly Lecture, "The Pro- and Antihypertensive Actions of the Kidney," will be presented by Dr. Eduardo Braun-Menendez, Buenos Aires, Argentina. Dr. Jonas E. Salk, Pittsburgh, will give the James D. Bruce Memorial Lecture, "The Immunologic Control of Paralytic Poliomyelitis." Symposiums are planned on influenza, electrolyte problems, radiation hazards, staphylococcal infections, genetics, aeromedical aspects of space flight, practical psychotherapy, and internal medicine. Special features include a concert, the annual banquet May 1, motion-picture sessions, a post-convention tour to Bermuda, and a ladies' program. Panel discussions, color-television medical clinics, and exhibits are planned. For information write Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates, Inc.: The American medical qualification examination to be given henceforth twice a year for foreign medical graduates. Medical Schools in the United States and Foreign Countries, Sept. 23. Final date for filing application is June 23. Executive Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Illinois.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 17-19. Sec., Dr. D. G. Gill, State Office Building, Montgomery 4.

ARIZONA:* *Examination and Reciprocity.* Phoenix, April 16-18. Exec. Sec., Mr. Robert Carpenter, 826 Security Bldg., Phoenix.

ARKANSAS:* *Examination.* Little Rock, June 5-6. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Written Examination.* San Francisco, June 16-19; Los Angeles, August 18-21; Sacramento, Oct. 20-23. *Oral Examination.* San Francisco, June 14; Los Angeles, August 16; San Francisco, November 15. *Oral and Clinical Examination for Foreign Medical School Graduates.* San Francisco, June 15; Los Angeles, August 17; San Francisco, November 16. Sec., Dr. Louis E. Jones, 1020 N Street, Sacramento.

COLORADO:* *Examination and Reciprocity.* Denver, June 10-11. Exec. Sec., Mrs. Beulah H. Hudgens, 715 Republic Bldg., Denver 2.

DELAWARE: *Examination and Reciprocity.* Dover, July 8-10. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

FLORIDA:* *Examination.* Miami, June 29-July 1. Sec., Dr. Homer L. Pearson, 901 N. W. 17th St., Miami.

GEORGIA: *Examination and Reciprocity.* Atlanta and Augusta, June. Sec., Mr. C. L. Clifton, 224 State Capitol, Atlanta.

IDAHO: *Examination.* Boise, July 14-16. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

INDIANA: *Examination.* Indianapolis, June 18-20. Exec. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

IOWA:* *Examination.* Iowa City, June 16-18. Exec. Sec., Mr. Ronald V. Saf, State Office Bldg., Des Moines 19.

KANSAS:* *Examination.* Kansas City, June 13-14. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

LOUISIANA: *Examination and Reciprocity.* New Orleans, June 5-7. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans.

MARYLAND: *Examination.* Baltimore, June 17-20. Sec., Dr. Frank K. Morris, 1211 Cathedral St., Baltimore 1.

MASSACHUSETTS: *Examination.* Boston, July 15-18. Sec., Dr. Robert C. Cochrane, Room 37 State House, Boston.

MICHIGAN:* *Examination.* Ann Arbor and Detroit, June 9-11. Sec., Dr. E. C. Swanson, 118 Stevens T. Mason Bldg., West Michigan Ave., Lansing 8.

MINNESOTA:* *Examination.* Minneapolis, April 15-17. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSOURI: *Examination.* St. Louis, May 30-31. Ex. Sec., Mr. John A. Hailey, Jefferson City.

NEBRASKA:* *Examination.* Omaha, June. Sec., Mr. Husted K. Watson, Room 1009, State Capitol Bldg., Lincoln 9.

NEW MEXICO:* *Examination and Reciprocity.* Santa Fe, May 19-20. Sec., Dr. R. C. Derbyshire, 227 E. Palace Ave., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York City and Syracuse, June 24-26. Sec., Dr. Stiles D. Ezell, 23 S. Pearl St., Albany.

NORTH CAROLINA: *Endorsement.* Asheville, May 5. *Examination.* Raleigh, June 16-19. *Endorsement.* Raleigh, June 17. Asst. Sec., Mrs. Louise J. McNeill, Professional Bldg., Raleigh.

NORTH DAKOTA: *Examination.* Grand Forks, July 9-11. *Reciprocity.* Grand Forks, July 12. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* June 19-21. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

OKLAHOMA:* *Examination.* Oklahoma City, June 3-4. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July 8-10. Acting Sec., Mrs. Marguerite G. Steiner, Box 911, Harrisburg.

SOUTH DAKOTA:* *Examination.* Rapid City, August 12-13. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TEXAS:* *Examination and Reciprocity.* Fort Worth, June 23-25. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 9-11. Director, Mr. Frank E. Lees, 324 State Capitol Bldg., Salt Lake City 1.

VIRGINIA: *Examination.* Richmond, June 12-14. *Reciprocity.* Richmond, June 11. Address: Board of Medical Examiners, 631 First St., S. W., Roanoke.

WASHINGTON:* *Examination.* Seattle, July 14-16. Administrator, Mr. Thomas A. Carter, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination and Reciprocity.* Charleston, July (date not set). Sec., Dr. N. H. Dyer, State Office Bldg., No. 5, Charleston.

WISCONSIN:* *Endorsement.* Madison, April 25. *Examination.* Milwaukee, July 8-10. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Bldg., 1 West Wilson St., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, June 2. Sec., Dr. Franklin D. Yoder, State Office Bldg., Cheyenne.

ALASKA:* On application in Anchorage and Juneau. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

GUAM: *Subject to Call.* Act. Sec., Dr. S. F. Provencher, Agana.

HAWAII: *Examination.* Honolulu, July 14-15. Sec., Dr. I. L. Tilden, 1029 Kapiolani St., Honolulu.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination.* Juneau, Nov. 4. Sec., Dr. R. Harrison Leer, Room 204, Alaska Office Bldg., Juneau.

ARKANSAS: *Examination.* Little Rock, May 5-6. Sec., Mr. S. C. Dellinger, Zoology Department, University of Arkansas, Fayetteville.

COLORADO: *Examination and Endorsement.* Denver, May 7-8. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

CONNECTICUT: *Examination and Endorsement.* New Haven, June 14. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

DISTRICT OF COLUMBIA: *Examination.* Washington, April 14-15. Deputy Director, Commission on Licensure, Mr. Paul Foley, 1740 Massachusetts Ave., N. W., Washington 6.

FLORIDA: *Examination.* Miami, June 7. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

KANSAS: *Examination.* Kansas City, June 3-4. Sec., Dr. R. E. Stowell, University of Kansas School of Medicine, Kansas City 12.

NEW MEXICO: *Examination.* Santa Fe, April 20. *Reciprocity.* Santa Fe, March 26. Sec., Mrs. Marguerite Cantrell, Box 1522, Santa Fe.

SOUTH DAKOTA: *Examination.* Vermillion, June 6-7. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

RHODE ISLAND: *Endorsement.* Providence, April 30. *Examination.* Providence, May 14. Administrator of Professional Regulation, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

TEXAS: *Examination.* April 18-19, Austin, Galveston and Houston. Sec., Bro. Raphael Wilson, 407 Perry Brooks Bldg., Austin.

WISCONSIN: *Examination.* Milwaukee, June 7. Sec., Mr. William H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

V 1
195

GOVERNMENT SERVICES

DEPARTMENT OF DEFENSE

Virchow Centennial at Armed Forces Institute of Pathology.—The centennial of the publication of Rudolph Virchow's "Cellular Pathology" is being celebrated throughout 1958 by the Armed Forces Institute of Pathology, Washington, D. C. The celebration program began March 3 with the first of a series of five daily lectures presented that week in Dart Auditorium. The scientific public was invited to attend these lectures. Other lectures in the series will be announced at suitable intervals.

Virchow's "Cellular Pathology," which first proclaimed a unified concept of cells as self-reproducing biological entities, was composed of a series of lectures which he gave in Berlin during 1858. Therefore, lectures from time to time at the Institute will stress specific applications to cellular pathology of current research in cytology, such as might be represented by histochemistry, biophysics, light and electron microscopy, tissue culture and virology, nutrition, immunology, ionizing radiation, tumors, and chemotherapy.

ATOMIC ENERGY COMMISSION

AEC Awards Research Contracts.—The U. S. Atomic Energy Commission has awarded 51 unclassified life science research contracts in the fields of medicine, biology, environmental sciences, radiation instrumentation, and special training. The contracts were awarded to universities and private institutions as part of the Commission's policy of assisting research and development in fields related to atomic energy as specified in the Atomic Energy Act of 1954, and as amended in 1956. Fifty contract renewals for one year each were awarded to allow for continuation of research already in progress. Twenty-one of these are in medical sciences, 23 in biology, 2 in environmental sciences, and 4 in radiation instrumentation.

NAVY

Training Course for Inactive Reservists.—A 14-day active duty training course in disease vector and economic pest prevention and control is available to inactive Reserve officers and enlisted medical department personnel beginning on the first Monday of April and June and the third Monday of May, 1958, at the Naval Disease Vector Control Center, Jacksonville, Fla.

Medical department Reservists from the First, Third, Fourth, Fifth, Sixth, Eighth, and Ninth Naval Districts are eligible, within funds available, for this training. Security clearance is not required. Interested eligible Reservists should submit their request to the Commandant of their home Naval District at the earliest practicable date.

Retired Officers.—The following U. S. Naval medical officers were placed on the retired list on March 1, 1958:

Rear Adm. Robert M. Gillett, after more than 34 years active service.
Capt. Charles W. Steele, more than 30 years active service.
Capt. George C. Thomas, more than 21 years active service.
Capt. Karl J. Palmberg, more than 20 years active service.
Capt. Jefferson Davis, more than 20 years active service.
Capt. David W. Sherwood, 16 years active service.

Personal.—Rear Adm. Bartholomew W. Hogan, surgeon general of the Navy, has been elected president of the Army and Navy Club of Washington, D. C. This is said to be the first time in the history of this 73-year-old club that a medical officer has been elected president.

VETERANS ADMINISTRATION

New Division on Research on Aging.—A new division of the Department of Medicine and Surgery in Washington, D. C., will conduct research in aging, survey the possibilities for research in retarding physical or mental deterioration, and coordinate the numerous studies of disorders associated with aging that are already under way in VA hospitals.

Dr. Charles C. Chapple, who will head the new division, said chemical, nutritional, psychological, biophysical, social, and clinical aspects will be considered, as these affect the individual.

The program will be developed under guidance of an advisory committee on problems of aging, comprising Ralph W. Gerard, M.D., professor of neurophysiology, Mental Health Research Institute, University of Michigan, chairman of the committee; Wendell H. Griffith, M.D., chairman, department of physiological chemistry, University of California School of Medicine; Eugene M. Landis, M.D., George Higginson professor of physiology, Harvard Medical School; Albert I. Lansing, Ph.D., chairman, department of anatomy, University of Pittsburgh School of Medicine; and William D. Stroud, M.D., professor of cardiology, Graduate School of the University of Pennsylvania.

PUBLIC HEALTH SERVICE

Many States Act to Increase Mental Health Services.—Dr. Robert H. Felix, director, National Institute of Mental Health, has reported an increase in mental health services over the United States as a result of laws passed by state legislatures in 1957. California, Minnesota, New Jersey, and Vermont passed laws providing grants-in-aid to localities for community mental health clinics, services for emotionally disturbed and mentally retarded children, rehabilitative and aftercare programs, alcoholism control programs, and public education on mental health.

These laws resemble the first legislation of this kind which was passed in New York in 1954, providing state grants on a dollar for dollar basis to help communities start new mental health programs or expand existing services. Connecticut, Pennsylvania, Indiana, Tennessee, and Florida passed grant-in-aid mental health legislation in 1955 and 1956. Laws authorizing counties to levy taxes or appropriate funds to support local mental health centers or clinics were passed by Iowa, Kansas, and South Dakota during 1957. Many states took steps to modernize their laws in regard to the commitment, detention and care, and treatment of the mentally ill. These included California, Colorado, Kansas, Minnesota, Montana, North Dakota, and Texas.

Connecticut, Maine, Minnesota, New Hampshire, Oregon, Rhode Island, and West Virginia took legislative action which ratified the Interstate Compact on Mental Health. This interstate agreement, first issued in 1955, makes the patient's welfare the cardinal consideration in deciding whether he shall be kept in one state or sent to another. Other states now participating in the Compact are Massachusetts, New Jersey, and New York.

Arkansas, Nebraska, and Texas authorized the construction of new institutions for care and treatment of the mentally retarded. Idaho and Minnesota made it mandatory for local school districts to provide instruction for handicapped children. A diagnostic and training center for the mentally retarded will be established in the state of Washington. New York is now developing plans for a state research institution on mental retardation.

In the state of Washington, a resident treatment center for emotionally disturbed children is being established at Western State Hospital where research as well as treatment will be carried on. Minnesota authorized a resident treatment center for emotionally disturbed children. In California, the Youth Authority is initiating a special program of intensive treatment in two institutions for juvenile delinquents.

Texas is planning to set up a new community hospital near the Texas Medical Center in Houston for training and research in mental illness. Iowa instituted a Mental Health Research Fund. A research program in alcoholism was established at the College of Medicine of Ohio State University. North Dakota directed the Medical Center of the University of North Dakota to encourage the training of psychiatric personnel for staffing the mental health agencies of the state and also provided training stipends.

Cancer Research.—The Public Health Service has announced a $229,481 contract with the Battelle Memorial Institute, Columbus, Ohio, to test chemicals and antibiotic filtrates as possible agents for use against cancer. The contract provides that the chemicals and antibiotic filtrates selected be used against three forms of cancer in mice, namely, leukemia, breast cancer, and a tumor of the connective tissue. In addition to searching for new agents to treat cancer, the Battelle Institute will seek improved methods for testing compounds, and will perform toxicity tests on antibiotic culture filtrates. If worthwhile and safe for humans, chemicals found through such work will be made available for studies in hospitals and clinics cooperating in a national cancer chemotherapy program.

Other laboratories now doing work on chemicals against cancer under similar contracts are Microbiological Associates, Bethesda, Md.; Wisconsin Alumni Research Foundation, Madison; Southern Research Institute, Birmingham, Ala.; Hazelton Laboratories, Falls Church, Va.; Stanford Research Institute, Menlo Park, Calif.; Arthur D. Little, Inc., Cambridge, Mass.; and Armour Research Foundation, Illinois Institute of Technology, Chicago. In addition to the National Cancer Institute, sponsors of the national chemotherapy research program include the American Cancer Society, the Damon Runyon Memorial Foundation, the Veterans Administration, the Atomic Energy Commission, and the Food and Drug Administration.

Research on Psychoactive Drugs.—Drugs that affect the brain and central nervous system are being studied in 79 research projects in mental hospitals, universities, and other research institutions throughout the United States, under the sponsorship of the National Institute of Mental Health of the Public Health Service. Grants for these projects total $1,685,219.

Most prominent among the studies being supported are clinical evaluations of drug effectiveness in schizophrenia, emotional disturbances of childhood, depressive states, and the neuroses. Other investigations being supported deal with (1) the effects of drugs on psychological functions; (2) the effects of drugs on animal behavior; (3) the effects of drugs on brain function; (4) the biochemical mechanisms of drug action; and (5) synthesis of new compounds.

Research Grants Awarded.—During February research grants and fellowships totaling $5,423,472 were awarded by the National Institutes of Health, Bethesda, Md. Scientists and institutions throughout the nation received 241 grants totaling $4,534,399 to support research in medical and related sciences. The fellowships support research training of students in medical, dental, nursing, and public health schools; candidates for master's and doctorate degrees in the biological sciences; and research scientists at various levels of training following receipt of the doctorate.

V 1
195

DEATHS

Cantor, William, Brooklyn; St. Louis University School of Medicine, 1925; associated with Maimonides Hospital; died Feb. 6, aged 58, of coronary thrombosis.

Cesteros, Jose Negron, New York City; Howard University College of Medicine, Washington, D. C., 1923; member of the Medical Society of the State of New York; associated with Park East and Manhattan General hospitals; died Feb. 8, aged 61, of coronary thrombosis.

Cole, Thomas Jonathan, Chicago; Howard University College of Medicine, Washington, D. C., 1928; died Feb. 17, aged 55, of portal cirrhosis with esophageal varices.

Elliott, John Robert ● St. Joseph, Mo.; Ensworth Medical College, St. Joseph, Mo., 1903; veteran of World War I; died in the Veterans Administration Hospital in Wadsworth Jan. 10, aged 84, of arteriosclerosis.

Eneboe, Paul Leo ● Bozeman, Mont.; University of Minnesota Medical School, Minneapolis, 1932; certified by the National Board of Medical Examiners; veteran of World War II; served as second vice-president of the Montana Tuberculosis Association; past-president of the staff of the Deaconess Hospital, where he died Jan. 9, aged 50, of coronary thrombosis.

Ericson, Charles E. ● Quincy, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1904; associated with the Blessing Hospital, where he died Feb. 5, aged 78, of arteriosclerotic heart disease.

Fallows, Howard Daniel ● Mason City, Iowa; State University of Iowa College of Medicine, Iowa City, 1905; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; died in Tucson, Ariz., Dec. 27, aged 74, coronary occlusion with myocardial infarction and arteriosclerotic heart disease.

Farr, Eri Madison ● Billings, Mont.; Medico-Chirurgical College of Philadelphia, 1908; specialist certified by the American Board of Preventive Medicine; member of the American Academy of General Practice and the Industrial Medical Association; served as county health officer; associated with the Billings Deaconess Hospital and St. Vincent's Hospital, where he was past-president of the staff; Civil Aeronautics Administration examiner; died in La Mesa, Calif., Feb. 9, aged 74, of heart disease.

Flake, Minna Margareta, New York City; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1915; member of the Medical Society of the State of New York; died in the Beekman-Downtown Hospital Feb. 10, aged 71.

Fritsch, Louis Ernest ● Indianapolis; Medical College of Ohio, Cincinnati, 1903; formerly practiced in Evansville, Ind., serving as president of the Vanderburgh County Medical Society and member of the board of health; veteran of World War I; died in the Methodist Hospital Jan. 20, aged 78, of burns received when he accidentally set fire to a chair while smoking.

Frolkis, Nathan Pinchos, Augusta, Ga.; Western Reserve University School of Medicine, Cleveland, 1936; service member of the American Medical Association; associated with the Veterans Administration Hospital, where he died Jan. 14, aged 45, of bronchogenic carcinoma.

Gale, Louis Harry ● Erie, Pa.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1925; died Jan. 18, aged 57.

Gallagher, Henry Joseph ● Providence, R. I.; Tufts College Medical School, Boston, 1917; veteran of World War I; on the staff of the Rhode Island, Charles V. Chapin, Roger Williams General, and Providence Lying-In hospitals; died in Akron, Ohio, Jan. 16, aged 66, of arteriosclerotic heart disease and bronchopneumonia.

Gants, Robert Tuthill ● Colonel, U. S. Army, Downs, Kan.; born in Cawker City March 14, 1905; University of Kansas School of Medicine, Kansas City, Kan., 1930; service member of the American Medical Association; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; adjunct clinical professor of surgery at the George Washington University School of Medicine in Washington, D. C.; entered the U. S. Army in 1934; served in the Philippines and at various military hospitals in this country until World War II, during which time he commanded station hospitals in France and Germany and received the Bronze Star, the Legion of Merit, and the Army Commendation Ribbon; chief of surgery, William Beaumont Army Hospital, El Paso, Texas;

● Indicates Member of the American Medical Association.

served as chief of surgery at the Walter Reed Army Hospital, Washington, D. C., where he died Feb. 15, aged 52, of carcinoma with multiple metastases.

Gaul, Julian Allen, Roxbury, N. Y.; Albany (N. Y.) Medical College, 1898; member of the Medical Society of the State of New York; county coroner; associated with the Aurelia Osborn Fox Memorial Hospital in Oneonta; died in the Margaretville (N. Y.) Hospital Jan. 30, aged 8[illegible], of pneumonia.

Georgetson, Socrates John, Pittsburgh; University of Pittsburgh School of Medicine, 1930; member of the American Academy of Dermatology and Syphilology; veteran of World War I; member of the staff of the Allegheny General Hospital; died Jan. 26, aged 57.

Giordano, Alfred Sabato • Sarasota, Fla.; born in Avellino, Italy, Feb. 3, 1893; Syracuse University College of Medicine, 1920; specialist certified by the American Board of Pathology; certified by the National Board of Medical Examiners; from 1945 to 1951 member of the House of Delegates of the American Medical Association and served as vice-chairman of the Section on Pathology and Physiology; member and for many years secretary-treasurer of the American Society of Clinical Pathologists; member of the American Association of Pathologists and Bacteriologists and the College of American Pathologists; entered the Mayo Foundation, Rochester, Minn., as a fellow in pathology in July, 1920; left in December, 1922; served on the staffs of the Elkhart (Ind.) General Hospital and Memorial and St. Joseph's hospitals in South Bend, Ind.; member of the board of editors of the *American Journal of Clinical Pathology;* died Feb. 15, aged 65, of coronary thrombosis.

Giragosian, Vahan H. J., Omaha; Reliance Medical College, Chicago, 1909; died in the Douglas County Hospital Dec. 20, aged 81, of arteriosclerotic heart disease with coronary insufficiency.

Goll, Alfred George, Stryker, Ohio; Northwestern University Medical School, Chicago, 1899; for many years member of the school board; a director of the Farmers State Bank; died in the Cameron Hospital, Bryan, Jan. 25, aged 85.

Gotwals, John Elmer • Phoenixville, Pa.; born in Yerkes Oct. 17, 1882; University of Pennsylvania School of Medicine, Philadelphia, 1911; for many years a member of the board of health of Phoenixville; served the community as school physician; at one time third vice-president of the Medical Society of the State of Pennsylvania and president of the Montgomery County Medical Society; veteran of World War I; his work in Boy Scouting won him the Silver Beaver Award for outstanding service to youth; for many years chief of surgery at the Phoenixville Hospital, where he died Feb. 7, aged 75, of carcinoma of the pancreas with metastasis to the lungs.

Graham, James Barnett, Jameson, Mo.; Barnes Medical College, St. Louis, 1897; on the staff of the Missouri Methodist Hospital, St. Joseph, where he died Jan. 12, aged 84, of arteriosclerotic heart disease and left bundle branch block.

Green, Austin L. • Milford, Ill.; Northwestern University Medical School, Chicago, 1907; associated with the Iroquois Hospital in Watseko, where he died Jan. 23, aged 88, of acute pericarditis and pneumonia.

Groehl, Henry Michael, Monterey, Mass.; Columbia University College of Physicians and Surgeons, New York City, 1895; an associate member of the American Medical Association; member of the Medical Society of the State of New York; died in Great Barrington Feb. 3, aged 85, of pneumonia.

Grotz, John George, Buffalo; University of Buffalo School of Medicine, 1914; an associate member of the American Medical Association; veteran of World War I; on the staff of the Lafayette General Hospital, where he died Jan. 20, aged 71, of heart disease and diabetes mellitus.

Gui, Weston Arch, Evanston, Ill.; Northwestern University Medical School, Chicago, 1951; interned at Evanston (Ill.) Hospital; served a residency at the Veterans Administration Hospital in Downey, Ill., and the Veterans Administration of the West Side Hospital, Chicago; served in the medical corps of the U. S. Army Reserve; service member of the American Medical Association; was shot and killed by a patient Jan. 31, aged 37.

Gustin, Genevieve • Jacksonville, Fla.; Woman's Medical College of Pennsylvania, Philadelphia, 1903; died Dec. 23, aged 78, of pyelonephritis and postradiation carcinoma of the cervix.

Gustin, Walter Sebre, Enfield, N. H.; University of Vermont College of Medicine, Burlington, 1897; died in Everett, Mass., Jan. 12, aged 83, of arteriosclerotic heart disease.

Hansen, John Robert, Santa Monica, Calif.; College of Medicine and Surgery, Chicago, 1910; died Jan. 17, aged 74, of coronary occlusion, and diabetes mellitus.

Hanson, Samuel, Stockton, Calif.; University of California School of Medicine, San Francisco, 1923; an associate member of the American Medical Association; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; died Jan. 18, aged 61, of myocardial infarction.

Hargreaves, James H. ✦ Conshohocken, Pa.; Temple University School of Medicine, Philadelphia, 1911; on the courtesy staff of Sacred Heart Hospital, Norristown, where he died Feb. 11, aged 68, of acute myocardial infarction.

Hawn, Chester Ellsworth, Temple City, Calif.; Hahnemann Medical College and Hospital of Philadelphia, 1920; died Feb. 6, aged 67, of coronary heart disease.

Heuschele, William Henry, San Jose, Calif.; Ensworth Medical College, St. Joseph, Mo., 1910; an associate member of the American Medical Association; for many years resident physician for the California State Athletic Commission; died Jan. 20, aged 73.

Horowitz, Israel S., New York City; Columbia University College of Physicians and Surgeons, New York City, 1903; died in the Mount Sinai Hospital Feb. 1, aged 77.

Hullsiek, Richard Benjamin, St. Paul; University of Minnesota Medical School, Minneapolis, 1924; service member of the American Medical Association; veteran of World Wars I and II; chief medical officer, Veterans Administration Center; died Feb. 1, aged 59, of coronary thrombosis.

Huntington, Robert Howard ✦ Fayetteville, Ark.; Atlanta College of Physicians and Surgeons, 1905; associated with Fayetteville City Hospital and Washington County Hospital; died Jan. 28, aged 78, of bronchopneumonia.

Kautz, Friedrich Gottfried ✦ New York City; born in Berlin, Germany, Jan. 29, 1889; Friedrich–Wilhelms–Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1912; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; formerly on the faculty of Cornell University Medical College; at one time director of radiology at the Desert Sanatorium of Southern Arizona in Tucson; director of radiology and roentgenology at the Knickerbocker Hospital; died Feb. 5, aged 69, of pulmonary fibrosis.

Kelly, Frank Lewis, Berkeley, Calif.; born in Oakland in 1884; University of California School of Medicine, San Francisco, 1912; member of the American Public Health Association, the California Academy of Medicine, the Sigma Xi and Delta Omega honor societies, the Delta Tau Delta fraternity, and other professional organizations; for many years on the faculty of the University of California; director of public health in Berkeley from 1923 to 1954, at one time associated with the state department of health; served on the board of directors of the Children's Hospital of the East Bay in Oakland; died in the Alta Bates Hospital Jan. 21, aged 73, of arteriosclerosis.

Kimball, Stockton ✦ Buffalo; born in Buffalo Aug. 17, 1902; University of Buffalo School of Medicine, 1929; dean and assistant professor of medicine at his alma mater; treasurer of the Association of American Medical Colleges; certified by the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Gastroenterological Association, Buffalo Academy of Medicine, American Society of Tropical Medicine, American Association for the Advancement of Science, American Malaria Society, Alpha Omega Alpha honorary fraternity, Sigma Xi scientific society, and Nu Sigma Nu medical fraternity; associated with Edward J. Meyer Memorial and Millard Fillmore hospitals, and Buffalo General Hospital, where he died Feb. 7, aged 55, of staphylococcic septicemia.

Kirkwood, George MacDonald, Syracuse, N. Y.; Syracuse University College of Medicine, 1938; veteran of World War II; died Jan. 25, aged 44.

Laferty, John Marshall ✦ Philadelphia; Jefferson Medical College of Philadelphia, 1912; veteran of World War I; director of obstetrical and gynecological service, St. Mary's Hospital, where he died Feb. 10, aged 67, of cerebrovascular accident and carcinoma of the bladder.

Lehrman, Philip Raphael ✦ New York City; born in Russia Oct. 12, 1895; Fordham University School of Medicine, New York City, 1918; clinical professor of psychiatry at New York University College of Medicine and the New York University Post-Graduate Medical School; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychoanalytic Association, American Psychosomatic Society, and the American Psychiatric Association; past-president of the New York Psychoanalytic Institute and Society; associated with the University Hospital; served on the staff of the Manhattan State Hospital; died Feb. 4, aged 62, of coronary thrombosis.

Lenz, Dorsey Soren, Big Fork, Mont.; Northwestern University Medical School, Chicago, 1922; fellow of the American College of Surgeons; served as health officer of Campbell County, Wyo.; associated with the Campbell County Memorial Hospital in Gillette; died in Gillette Feb. 2, aged 64, of coronary occlusion.

Light, John Joseph ✦ Lebanon, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1897; specialist certified by the American Board of Radiology; member of the American College of Radiology; served as county coroner, deputy coroner, and county treasurer; associated with the Good Samaritan Hospital; died Feb. 2, aged 84, of myocardial infarction.

Littman, Sidney, Santa Barbara, Calif.; Western Reserve University School of Medicine, Cleveland, 1918; for many years practiced in Cleveland, where he was associated with the Mount Sinai Hospital; died Jan. 19, aged 67.

Livermore, Denny Wood ✦ Foxboro, Mass.; Boston University School of Medicine, 1906; for many years school physician and town physician; associated with Foxboro State Hospital; died Jan. 15, aged 85, of heart disease.

Lombardi, Nicholas Thomas, Amsterdam, N. Y.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1920; an associate member of the American Medical Association; past-president of the Montgomery County Medical Society; associated with Amsterdam Hospital and St. Mary's Hospital, where he died Jan. 16, aged 74, of coronary insufficiency.

McGowan, Donald Oscar ✦ Carmichael, Calif.; University of Oregon Medical School, Portland, 1934; member of the American Academy of General Practice; veteran of World War II; burned to death in his car Feb. 3, aged 50.

Madden, Owen Michael ✦ Buffalo; Queen's University Faculty of Medicine, Kingston, Ontario, Canada, 1919; served overseas during World War I; for many years on the staff of the Lafayette General Hospital, where he was vice-president of the board of directors, and where he died Jan. 30, aged 68, of cardiac failure.

Mansifee, William H., St. Louis; Chicago Homeopathic Medical College, 1889; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1893; at one time public school hygiene inspector; an organizer of the Provident Hospital which later became Peoples Hospital; died Feb. 7, aged 93.

Mason, Claude Hutchinson ✦ El Paso, Texas; Maryland Medical College, Baltimore, 1911; specialist certified by the American Board of Radiology; member of the American College of Radiology; veteran of World War I and received the Distinguished Service Cross, Legion of Honor, and the Croix de Guerre with Palm and Star; associated with the Federal Correctional Institution Hospital in La Tuna, and the Hotel Dieu Hospital, where he died Jan. 13, aged 72, of metastatic carcinoma of the lungs, skin, and hands.

Morris, Louis C. ✦ Chicago; Rush Medical College, Chicago, 1928; assistant professor of medicine at Northwestern University Medical School; specialist certified by the American Board of Internal Medicine; member of the American College of Chest Physicians and the American Trudeau Society; veteran of World War II; associated with Cook County and Grant hospitals, and the Weiss Memorial Hospital, where he died Feb. 23, aged 57, of myocardial infarction.

O'Neil, James Charles ✦ Burlington, Vt.; University of Vermont College of Medicine, Burlington, 1917; served on the faculty of his alma mater; specialist certified by the American Board of Psychiatry and Neurology; fellow of the American Psychiatric Association; veteran of World War II; formerly member of the staff of the Vermont State Hospital in Waterbury, where he was superintendent from 1936 to 1944; assistant superintendent of the Brattleboro (Vt.) Retreat, from 1947 to 1949; died in the De Goesbriand Hospital Jan. 23, aged 73, of cancer.

Paryzek, Harry Vincent ✦ Cleveland; born in Cleveland Jan. 11, 1892; Western Reserve University School of Medicine, Cleveland, 1915; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the House of Delegates of the American Medical Association from 1942 to 1945; served as secretary-treasurer and president of the Cleveland Academy of Medicine, which in 1950 gave him its award for distinguished service to the profession and community; past-president of the Ohio State Medical Association; at one time on the faculty of his alma mater; served overseas during World War I; member of the Cleveland Medical Library Board; associated with St. Alexis Hospital; died Jan. 20, aged 66, of cardiac hypertrophy and ventricular fibrillation.

Patterson, Benjamin Howard, Bay Pines, Fla.; University of Pittsburgh School of Medicine, 1900; veteran of World War I; died in the Veterans Administration Center Dec. 19, aged 81, of arteriosclerotic heart disease.

Pavy, Odra S. ✦ Laramie, Wyo.; University of Cincinnati College of Medicine, 1922; retired Union Pacific Railroad surgeon; associated with the Ivinson Memorial Hospital; died Jan. 21, aged 71, of arteriosclerosis and cardiac failure.

Roberts, Elisha Houston, Corsicana, Texas; University of Oklahoma School of Medicine, Oklahoma City, 1916; died in Veterans Administration Center, Temple, Nov. 8, aged 65.

Robinson, William Briscoe, Los Angeles; Medical College of Ohio, Cincinnati, 1896; died Jan. 22, aged 90.

Roddy, John Augustus ✦ Oklahoma City, Okla.; Jefferson Medical College of Philadelphia, 1907; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; at one time on the faculty of his alma mater; associated with St. Anthony's Hospital; died Jan. 1, aged 73, of coronary occlusion.

V 1
195

Rohrer, William M., Springtown, Texas; University Medical College of Kansas City, Mo., 1907; died in the All Saints Hospital, Fort Worth, Dec. 15, aged 72.

Rossman, Morris Munice ✱ Freeport, N. Y.; Syracuse University College of Medicine, 1934; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; veteran of World War II; served on the staffs of University Hospital in New York City and the South Nassau Communities Hospital in Oceanside; associated with Doctors Hospital, where he died Feb. 3, aged 48, of injuries received in an automobile accident.

Rupp, William A. ✱ Chicago; Northwestern University Medical School, Chicago, 1900; associated with the South Shore Hospital; died in the Veterans Administration Hospital in Hines, Ill., Feb. 4, aged 81, of coronary arteriosclerosis.

Sakin, Benjamin M. ✱ Brooklyn; Fordham University School of Medicine, New York City, 1917; member of the staff of the Brooklyn Jewish Hospital; medical columnist for the Jewish Daily Forward; died Feb. 17, aged 71, of a heart attack.

Schantz, John Philip, Schuylkill Haven, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1946; interned at the Sacred Heart Hospital in Allentown; served in the Korean War; formerly a resident physician at the Charles H. Miner Sanatorium in Hamburg; on the staff of the Pottsville (Pa.) Hospital; member of the American Trudeau Society; died Jan. 27, aged 37, of myocardial infarction.

Schier, Anton Robert, Dallas, Texas; Gross Medical College, Denver, 1893; veteran of World War I; formerly an officer in the regular U. S. Navy; at one time medical superintendent of the State Hospital for Epileptics and School for Feebleminded at Woodward, Iowa; died Nov. 12, aged 82.

Schweninger, Edward A., St. Louis; Washington University School of Medicine, St. Louis, 1907; for many years associated with the City Hospital, where he died Feb. 4, aged 79.

Sealy, Albert Henry ✱ Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1912; associated with Mercy and St. Ann's hospitals, and the Grant Hospital, where he died Jan. 15, aged 75, of pneumonia.

Shepard, George Wanzor ✱ Captain, U. S. Navy, retired, Vallejo, Calif.; born June 11, 1878; Western Reserve University Medical Department, Cleveland, 1903; service member of the American Medical Association; fellow of the American College of of Surgeons; appointed assistant surgeon in the Navy with the rank of lieutenant (jg) in 1907; during World War I served aboard two naval ships and at the Naval Training Station, Norfolk, Va.; from 1935 to 1937 served with the Marine Detachment, American Legation, Peiping, China; attained the rank of captain in 1929; reaching the statutory age for retirement in 1942, was placed on the retired list after more than 35 years naval service; died in the U. S. Naval Hospital, Oakland, Feb. 3, aged 79.

Sherman, Relza Newton ✱ Bradenton Beach, Fla.; University of Tennessee College of Medicine, Memphis, 1913; member of the Michigan State Medical Society; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; formerly practiced in Bay City, Mich., where he was associated with the Mercy and General hospitals; died Jan. 16, aged 70.

Shrum, Riley, Los Angeles; University of Louisville (Ky.) Medical Department, 1898; died Jan. 29, aged 83.

Simon, Frederick ✱ New York City; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, 1915; died Dec. 30, aged 69, of a heart attack.

Smith, Charles Hervey, Uniontown, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1893; an associate member of the American Medical Association; fellow of the American College of Physicians; veteran of World War I; associated with Uniontown Hospital; died Jan. 20, aged 90, of arteriosclerotic heart disease.

Smith, Conrad, St. Petersburg, Fla.; Boston University School of Medicine, 1899; professor emeritus of laryngology at his alma mater; fellow of the American College of Surgeons; died Dec. 19, aged 84, of coronary occlusion, and arteriosclerosis.

Smith, Herbert Beekman, Corning, N. Y.; University and Bellevue Hospital Medical College, New York City, 1899; an associate member of the American Medical Association; on the staff of Corning Hospital; formerly county coroner; died in St. Joseph's Hospital, Elmira, Jan. 30, aged 81.

Smith, Robert Benjamin ✱ Akron, Ohio; Ohio State University College of Medicine, Columbus, 1940; specialist certified by the American Board of Internal Medicine; member of the American College of Allergists; on the staff of St. Thomas Hospital; died Feb. 2, aged 42.

Stanbery, Albert Russel, Vandalia, Ill.; St. Louis College of Physicians and Surgeons, 1909; died in the Fayette County Hospital Dec. 6, aged 82, of acute yellow atrophy of the liver and arteriosclerosis.

Steinman, William ✱ Miami, Fla.; born in Chicago Sept. 19, 1916; University of Illinois College of

Medicine, Chicago, 1941; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; clinical assistant professor of ophthalmology at the University of Miami School of Medicine in Coral Gables; president of the Dade County Eye, Ear, and Nose Society; veteran of World War II; associated with the Mount Sinai Hospital in Miami Beach, and Mercy and Jackson Memorial hospitals; formerly practiced in Chicago; died Feb. 10, aged 41, of a heart attack.

Stewart, William Lloyd ✦ Mediapolis, Iowa; State University of Iowa College of Medicine, Iowa City, 1907; associated with the Burlington (Iowa) Hospital, where he died Dec. 27, aged 71.

Stilson, George Doremus, Long Beach, Calif.; Cornell University Medical College, New York City, 1908; an associate member of the American Medical Association; member of the American Urological Association; specialist certified by the American Board of Urology; past-president of the Long Beach Branch of the Los Angeles County Medical Society; past-president of the Los Angeles County Urological Society; associated with Seaside, St. Mary's, and Community hospitals; died Jan. 22, aged 71, of cancer.

Stofer, Er Stanton, Kansas City, Mo.; University Medical College of Kansas City, Mo., 1910; veteran of World War I; died Feb. 15, aged 71.

Stover, John Franklin ✦ Doe Hill, Va.; University College of Medicine, Richmond, 1912; staff member, King's Daughters Hospital in Staunton; died Jan. 12, aged 76, of coronary occlusion.

Strausbaugh, James Nelson ✦ Meadville, Pa.; Western Reserve University School of Medicine, Cleveland, 1930; member of the American Academy of General Practice; charter member of the staff of Spencer Hospital; died in the Arnot Ogden Memorial Hospital, Elmira, Jan. 24, aged 53, of acute hemorrhagic pancreatitis.

Strauss, Maurice Jacob ✦ New Haven, Conn.; born in New Haven Jan. 3, 1893; Columbia University College of Physicians and Surgeons, New York City, 1917; specialist certified by the American Board of Dermatology and Syphilology; member of the American Academy of Dermatology and Syphilology; clinical professor emeritus of dermatology at Yale University School of Medicine; director of venereal disease bureau, New Haven Health Department, 1922-1946; veteran of World War I; associated with the Grace Hospital, Hospital of St. Raphael, and New Haven hospitals; consultant, Laurel Heights State Tuberculosis Sanatorium in Shelton, Veterans Administration Hospital in Newington, Griffin Hospital, Derby, New Britain (Conn.) Hospital, and the Norwich (Conn.) State Hospital; died Feb. 2, aged 65, of thrombosis of cerebellar artery.

Suldane, John Anthony ✦ Chicago; St. Louis University School of Medicine, 1910; associated with St. Elizabeth Hospital, where he died Feb. 6, aged 72, of coronary artery heart disease.

Sullivan, Henry Bradley, Shawnee, Kan.; University of Kansas School of Medicine, Kansas City, Kan., 1920; member of the American Academy of General Practice; president-elect of the Kansas Academy of General Practice; member and past-president of the staff, Bethany Hospital, where he died Jan. 17, aged 61.

Sullivan, John Morgan, Sanger, Texas; Fort Worth School of Medicine, Medical Department of Texas Christian University, 1910; health officer; associated with the Flow Memorial Hospital in Denton, where he died Feb. 1, aged 72, of cerebral hemorrhage.

Sutton, Harris Raymond ✦ Hoffman, Minn.; University of Minnesota Medical School, Minneapolis, 1916; formerly served in the medical corps of the regular Navy; member of the school board; served as village mayor and council member; associated with Our Lady of Mercy Hospital and Douglas County Hospital in Alexandria, where he died Jan. 16, aged 69, of carcinoma of the lung with cerebral metastases.

Swanson, Gordon Rudolph ✦ Naperville, Ill.; Northwestern University Medical School, Chicago, 1925; fellow of the American College of Surgeons; associated with Oak Park (Ill.) Hospital and Hinsdale (Ill.) Sanatorium and Hospital; died in the Passavant Memorial Hospital, Chicago, Feb. 18, aged 58, of lobar pneumonia and influenza.

Tell, Abram Batt ✦ Worcester, Mass.; Kansas City (Mo.) University of Physicians and Surgeons, 1944; medical director of the Doctors Hospital, where he died Feb. 1, aged 55, of acute coronary thrombosis.

Thompson, Edward Cameron, Wellesley, Mass.; born in Walden, N. Y., Oct. 19, 1875; Columbia University College of Physicians and Surgeons, New York City, 1901; member of the Medical Society of the State of New York; an associate member of the American Medical Association; fellow of the American College of Surgeons; formerly practiced in Newburgh, N. Y., where he was past-president of the Orange County Medical Society, for many years member of the school board, and on the staff of St. Luke's Hospital; served on the staff of the Cornwall (N. Y.) Hospital; consulting surgeon at the Goshen (N. Y.) Hospital; veteran of World War I; died Jan. 3, aged 82.

Traxler, Paul Scoville, Granada Hills, Calif.; University of Illinois College of Medicine, Chicago, 1914; service member of the American Medical Association; veteran of World War I and II; formerly manager of the Veterans Administration Hospital in Phoenix, Ariz.; died in the Veterans Administration Center, West Los Angeles, Jan. 18, aged 65.

Urban, Kay Bonner • Tyler, Texas; University of Pennsylvania School of Medicine, Philadelphia, 1919; member of the American Academy of General Practice; at one time medical director of the Gonzales Warm Springs Foundation Hospital in Gonzales; on the staff of the East Texas Tuberculosis Sanatorium; died Jan. 24, aged 63, of aortic stenosis.

Walker, James Clyde, Obion, Tenn.; University of Tennessee College of Medicine, Memphis, 1924; member of the Tennessee State Medical Association; died in the Obion County General Hospital, Union City, Nov. 16, aged 64, of coronary occlusion.

Walton, Robert Ralph • Paradise, Calif.; George Washington University School of Medicine, St. Louis, 1916; member of the American Academy of General Practice; on the staff of St. Francis Hospital in Lynwood; died in Lincoln Jan. 4, aged 67, of rupture of the mesenteric artery and arteriosclerosis.

Watt, Charles Hansell • Thomasville, Ga.; Johns Hopkins University School of Medicine, Baltimore, 1912; member of the founders group of the American Board of Surgery; fellow of the American College of Surgeons and past-president of the Georgia Chapter; member of the Southern Surgical Association; past-president of the Atlantic Coast Line Surgeons; veteran of World War I; senior surgeon at John D. Archbold Memorial Hospital; died Jan. 27, aged 71, of cerebral hemorrhage.

Watters, Marcus Henry, Helena, Mont.; George Washington University School of Medicine, Washington, D. C., 1905; at one time associated with the public health department in Washington, D. C.; formerly on the staffs of the Veterans Administration hospitals in Fort Harrison, Mont., Whipple, Ariz., and Wichita, Kan.; died in St. John's Hospital Jan. 29, aged 80, of pneumonia.

Webb, Jeff Newton • Seneca, S. C.; Emory University School of Medicine, Atlanta, 1915; member of the Southeastern Surgical Congress; veteran of World War I; died in the Oconee Memorial Hospital Jan. 12, aged 66.

Webb, Walter Reeves • Hampshire, Tenn.; University of Nashville (Tenn.) Medical Department, 1900; associated with the Maury County Hospital in Columbia; died Dec. 10, aged 86, of cerebral hemorrhage.

Wells, Clarence Edgar, Oakhurst, Calif.; University of California School of Medicine, San Francisco, 1915; died in Visalia Jan. 28, aged 73, of cerebral thrombosis and polycythemia.

Werner, August C. L. • Cincinnati; University of Louisville (Ky.) Medical Department, 1908; formerly superintendent of the Dayton (Ohio) State Hospital; died in the Good Samaritan Hospital Jan. 13, aged 77, of perforated duodenal ulcer.

White, Willard Justin • Longmont, Colo.; Barnes Medical College, St. Louis, 1896; veteran of World War I; served on the school board for 20 years and was its president for 10 years; team physician for Longmont High School athletic squads; associated with St. Vrain Hospital, where he died Jan. 20, aged 85, of chronic myocarditis and arteriosclerosis.

Wood, W. Franklin, Belmont, Mass.; born in Patchogue, N. Y., Nov. 19, 1890; New York Homeopathic Medical College and Hospital, New York City, 1912; Tufts College Medical School, Boston, 1917; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association and the Massachusetts Medical Society; served as president and secretary of the Massachusetts Hospital Association and of the New England Hospital Assembly, regent of the American College of Hospital Administrators, and president of the New England Superintendents Club; formerly secretary and vice-president of the Massachusetts Psychiatric Society; formerly affiliated with the Massachusetts General Hospital, Massachusetts Department of Mental Health, Boston Psychopathic Hospital, the Massachusetts Memorial Hospitals in Boston, the Monson State Hospital in Palmer, and the Danvers (Mass.) State Hospital; retired as director of the McLean Hospital in Waverley in 1956; psychiatric consultant at the Massachusetts Department of Mental Health and at the Leslie Junior College in Cambridge; school physician at the Belmont schools and health officer; veteran of World War I; served as a director of the Waverley Cooperative Bank and a trustee of the Belmont Savings Bank; died Jan. 15, aged 67, of heart disease.

Wood, Murray • Andrews, Texas; University of Texas School of Medicine, Galveston, 1939; died Jan. 23, aged 45.

Yakulis, Casimir Walter Jr. • Vandergrift, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1939; veteran of World War II; on the staff of the Allegheny Valley Hospital in Tarentum; died Feb. 1, aged 45, of coronary occlusion.

Yoder, Jacob Alexander • Mansfield, Ohio; University of Wooster Medical Department, Cleveland, 1898; associated with the Mansfield General Hospital; died Jan. 30, aged 88.

FOREIGN LETTERS

AUSTRIA

Tuberculous Meningitis and Miliary Tuberculosis.—At the meeting of pediatricians at the Van Swieten Convention in Vienna in September, Dr. H. E. Lorenz said that despite a marked decrease of the incidence of tuberculosis in childhood, particularly of the generalized hematogenous forms, early diagnosis still plays an all-important part in the prognosis of those with tuberculous meningitis and miliary tuberculosis. Its value was fully illustrated by the fact that most patients of all ages were cured if treatment was started early. The speaker emphasized the triad of headache, vomiting, and constipation in the early diagnosis of tuberculous meningitis in infants and children of school age. On the other hand the course of the fever is variable; in 50% of the patients the temperature was between 37 and 38.5 C (98.6 and 100.5 F). Such "classic" early symptoms as fatigue, lassitude, and irritability were observed in only 18% of the infants hospitalized at the Children's Hospital of the University of Graz and in only 6% of the older children. As regards other early symptoms, only spasms may be considered pathognomonic. The tuberculin test proved to be most reliable, being positive in 97% of the cases.

Studies on Children After Tuberculous Meningitis.—At the same meeting Dr. H. E. G. Huber reported a series of 33 children who had had tuberculous meningitis. In most of the patients the disease had occurred five years earlier. Changes in the eye grounds, cochleovestibular damages, and unilateral paresis were essentially as described by other observers, but, contrary to previous findings, intracranial calcification was not only present in patients with severe impairment but also in two cured children without other detectable defects. Likewise, the results of electroencephalographic studies showed no correlation with the earlier severity of the disease. Children with somatic defects without exception also showed mental deterioration; 24 of those who were apparently completely cured manifested more or less severe disturbances of the autonomic nervous system, affectivity, and single intelligence factors and had neuropathic and neurotic symptoms. Disturbances in affect consisted in severe emotional lability, complete absence of inhibition, or impoverishment of personality. Diminished capacity of concentration and association was found in several children despite a normal general intelligence. In a few patients the inherited features evolved in an exaggerated and distorted form. It was concluded that occupational therapy should be given after tuberculous meningitis.

Tetany.—At the same meeting Dr. H. E. Zweymüller classified tetany as hypocalcemic or normocalcemic. The first group included rachitogenic, parathyroid, and calciprivic tetany; tetany due to primary calcipenia or to chemical absorption of blood calcium; and tetany associated with kidney diseases. The second group included idiopathic tetany, occasional tetanic spasms, hyperventilation tetany, tetany associated with intoxication and infection, tetany associated with organic changes of the brain, chlorprivic tetany, and pseudotetany. Dr. H. G. Fanconi said that the cause of tetany in patients with normal blood calcium level was first believed to be based on a decrease of ionization of blood calcium possibly influenced by alkalosis. Later it was gradually recognized that it may be due to hyperphosphatemia, hyperkalemia, or hypermagnesemia. It has been demonstrated on one hand that hyperpotassemia promoted the manifestation of hypocalcemic tetany and on the other hand that manifestation of hypocalcemic tetany may be prevented in the newborn child by inducing hypopotassemia. Several forms of tetany have been detected in which it was not possible to demonstrate any change in blood chemistry. The cause might be found in the intracellular rather than in the extracellular fluid.

Tetany is a syndrome with many causes. Rickets on the one hand may lead to tetany and on the other hand also to parathyroid hypertrophy. The response to therapy is different in patients with parathyroid tetany and those with rachitogenic tetany. Patients with parathyroid tetany responded readily to dihydrotachysterol, but patients with rachitogenic tetany did not. The healing of the rachitic process started and the blood calcium level was restored to normal only when dihydrotachysterol was given and vitamin D discontinued. The opposite did not hold. Patients with chronic hypoparathyroidism might have good results from the much less costly treatment with vitamin D than with dihydrotachysterol. There seems to be a regulatory center in the brain for calcium and phosphorus metabolism. An American physician has suggested that hypercalcemia which occasionally may be observed in patients with poliomyelitis

The items in these letters are contributed by regular correspondents in the various foreign countries.

is the consequence not only of inactivity but also of a paralysis of the centers in the diencephalon. The speaker observed a newborn infant with severe brain damage who in the first month of life had a marked hypocalcemia associated with tetany. This supports the theory that there is a center for the regulation of calcium and phosphorus that may be subject to injury.

Infantile Epilepsy.—At the same meeting Dr. H. H. Asperger said that with the general increase of cerebral disturbances in childhood, the incidence rate of epilepsy has markedly increased. Differential diagnosis of the various types of infantile epilepsy may be difficult. Spastic conditions may arise from various causes and later prove to be harmless. The electroencephalogram has become one of the most important diagnostic devices but the results should always be evaluated in connection with the clinical findings.

Rickets.—At the same meeting Dr. H. O. Jurgensen said that although by improved diagnostic procedures more distinct delimitation has been made between true rickets due to vitamin deficiency and the complex group of treatment-resistant rickets, and although in the latter group some types have been differentiated, the relationship between the intermediary calcium and phosphorus metabolism has not been completely elucidated. The frequency of rickets in the rural and city areas, even if the cases are mostly mild, indicates that the organization for the prevention of rickets is defective and will remain so as long as the administration of vitamin D to nurslings depends on the voluntary visit of a member of the welfare service or of a physician. To provide for an extensive program of prevention starting as early as possible, it was proposed that all pregnant women be supplied with vitamin D in the last months of pregnancy. This would benefit both mother and child. Additional postnatal preventive measures would, however, still be required. One such measure is the fortification of milk with vitamin D_3 and A. Such milk is also beneficial for the elderly who because of an absorptive insufficiency have an increased need of vitamins. Steps must be taken, however, to prevent hypervitaminosis in persons taking vitamin supplements.

Vomiting in Nurslings.—At the same meeting Dr. H. J. Siegel said that he gave chlorpromazine to 16 infants with hypertrophic pyloric stenosis. Of these 11 were cured, and 5 had to be operated on. Treatment was started with chlorpromazine alone in 13 nurslings and this brought about cures in 8 patients. Of the five patients in whom no response was obtained, one was immediately operated on; in the other four, combined treatment with chlorpromazine and atropine methylnitrate was used. This was successful in only one infant, and the other three had to be operated on. Two of the infants who did not respond to treatment with atropine methylnitrate alone were cured by the combined therapy. One infant who was given the combined treatment from the beginning had to be operated on. Treatment with chlorpromazine was highly effective in patients with habitual vomiting, but the administration of this drug should be reserved for patients with unusual restlessness and increased tonus in whom the ataractic effect of this drug is desirable. In all the rest of the patients a processed carob flour preparation (Arobon) is indicated as it combines the advantages of prompt effectiveness with a safe and simple administration.

Cerebral Angiography in Children.—At the same meeting Drs. H. K. Kundratitz and E. Zweymüller reported on the visualization of the course and distribution of the cerebral vessels with the aid of angiography. Abnormal air spaces over the hemisphere indicate atrophy following trauma. In such patients one finds that, contrary to normal, the cerebral arteries do not extend to the internal lamina. The absence of blood supply in circumscribed areas proves the presence of a defect. Cerebral cysts, porencephalitis, and hydrocephalus give diagnostic findings. The absence of the angulation of the anterior cerebral artery, extension of the vessels, or a change in the so-called syphon may be also considered as pathological. Supplementing information obtained by pneumoencephalography and electroencephalography, cerebral angiography plays an important part in diagnosis.

Dr. H. E. Klausberger reported the results obtained by cerebral and cerebellar angiographic studies in 78 children under 14 years of age who had suffered brain damage. A practicable anesthesia is a prerequisite for the success of this procedure. At the second Surgical University Clinic in Vienna, Austria, thoracic and abdominal angiography was performed under a modified method of anesthesia. No complications were observed during such examinations. The contrast medium used was sodium acetrizoate; 5 cc. of a 35% solution of this agent was injected into infants and small children up to the age of five years. In older children a 50% solution was used. The removal of the injection cannula should be followed by applying firm and prolonged pressure over the vessel and the patient should be observed until he awakens.

Special Facilities for Premature Infants.—At the same meeting Dr. H. H. Gross said that all premature infants weighing less than 1,800 Gm. (4 lb.) should be placed in a special ward that would meet the requirements for a sterile environment and provide specially trained nurses. There should be separate wards for those born in hospitals and for

those born at home. Sick premature infants should be placed in an isolation ward. The immediate transportation of premature infants in portable incubators to the premature ward is essential. During the use of incubators the least possible additional supply of oxygen should be given in order to prevent the occurrence of retrolental fibroplasia.

Anemia in the Premature Infant.—At the same meeting Dr. H. G. Weippl said that in the treatment of anemia in the premature infant it is necessary to distinguish between the first phase of normochromic and the second phase of hypochromic anemia. The first phase lasts up to the 10th month of life and may be due to a retrogressive extramedullary erythropoiesis, or an increased destruction of the fetal hemoglobin-bearing macrocytes. A causal therapy is, therefore, not possible, but blood transfusions and cobalt may be indicated. Forty premature infants were treated with an organic compound of iron, cobalt, and copper, and 36 were cured. There was no iron deficiency, therefore treatment with iron alone could not have been effective. The second phase of anemia is due to a too small iron deposit in the premature infant, which distinguishes it from nutritional anemia. Prevention of this anemia is still unsatisfactory. An average hemoglobin value of 44% was observed in 40 premature infants between the ages of 6 and 18 months. In contrast to the first phase, the second phase is progressive and may lead to a severe or fatal anemia. The oral administration of iron, however, brings about a prompt cure, and the occurrence of anemia may be prevented if treatment is started early enough (in the third month at the latest).

Recurrent Parotitis.—At the same meeting Dr. H. P. Krepler reported on 13 patients with recurrent pyogenic swelling of the parotid gland. In order to differentiate this disease from mumps and from chronic glandular or interstitial processes, it is essential to examine the secretion and to obtain a sialogram. During the acute phase of the disease the secretion is mucopurulent, but in the remissions it is white, flocculent, and slightly turbid. This flocculent cloudiness is best seen when the secretion is drained through a cannula into a test tube. Even if the swelling is unilateral the roentgenograms usually show a bilateral, grape-like cystic enlargement of the end-ramification of the duct system. These changes were distinctly and fully demonstrated on both sides, during the first unilateral attacks, in an infant at the age of 16 months. In contrast to a previous concept these observations favor the belief that the roentgenologic changes in the duct system are not primarily the sequel of chronic inflammation but represent an anatomic factor (congenital sialodochiectasis) which facilitates the invasion of the parotid duct system by bacteria of the oral cavity. Such other factors as the bacterial content of the oral cavity, the patient's resistance, and the secretion and discharge of saliva must also be considered. The condition of the opening of the Stenson's duct, which was larger than usual in all these patients, may be a contributing factor. This concept does not rule out the occurrence of secondary destructive changes or of the distention of the duct system arising from a local inflammatory process. Antiseptic mouthwashes, the instillation of antibiotics, and the general treatment with phenoxymethyl penicillin were recommended.

Infectious Diseases.—At the same meeting Dr. H. H. Zischinsky reported on the changes in the incidence of acute infectious diseases in the last decades. This is especially true for diphtheria which has almost entirely disappeared. In 1956 only 56 diphtheria cases were reported in Vienna. Scarlet fever is now so devoid of complications that it hardly deserves to be called a disease. No death resulted from scarlet fever in 1956 in Vienna, and scarlatinal nephritis is a rarity. The enteric infections occur with about the same frequency but are much milder. Measles and whooping cough have lost much of their previous dangerous character. In contrast the prevalence of virus infections, particularly those due to the neurotropic viruses, has increased.

INDIA

Intrapleural Pressure in Lung Abscess.—P. N. Laha (*Journal of the Association of Physicians of India*, vol. 6, January, 1958) recorded the intrapleural pressure on the affected side in 23 patients with lung abscess. The normal intrapleural pressure was −14 to −3 cm. H_2O on inspiration and −10 to 0 cm. H_2O on expiration. In 15 of the patients the pressure was within normal limits on inspiration and in 10 it was normal on expiration. The roentgenograms of the chest in all these patients were negative except for the evidence of lung abscess. The abscess per se did not affect the elasticity of the lung which is important in the normal functioning of the organ. In seven patients the pressure was less than −3 cm. H_2O on inspiration and in seven it was positive on expiration. In all these except one, as evidenced radiologically, the abscess was surrounded by pneumonitis of varying dimensions, and some in addition had the clinical signs of pulmonary emphysema. In these cases, therefore, the pneumonitis by itself or in combination with emphysema was responsible for reducing the intrapleural pressure on inspiration and changing it to positive on expiration. In one patient in whom no such changes were apparent but in whom the pressure was positive on

expiration, possibly the changes of emphysema were not advanced far enough to be detected clinically.

Pneumonitis damages the elasticity of the lung and interferes with the intrapleural pressure. Emphysematous lungs are overdistended and the residual volume is increased, thus altering the elasticity of the lung. In four patients the pressure was within the normal range in one phase of respiration and altered in the other. Here there may have been only a partial impairment of elasticity. In three patients the pneumothorax needle introduced through the fifth intercostal space failed to record the intrapleural pressure in either phase of respiration, but when introduced through the second intercostal space the pressure was recorded. In two patients it could not be recorded in any phase of respiration when the pleural space was approached through the fifth, fourth, third, and second intercostal space. This may be explained by the occurrence of pleural reaction resulting in adherent pleura, the reaction being intensive but localized in the first three patients in whom the obliteration of the pleural space was limited, but intensive and extensive in the latter two patients in whom the pleural cavity was obliterated over a wider area. The mean intrapleural pressure showed variations from the normal which reflected the variations of the inspiratory and expiratory intrapleural pressure. The side and site of the abscess did not produce any significant alteration in the intrapleural pressure. The duration of the abscess per se did not affect the intrapleural pressure.

Bronchonasal Allergy in Children.—S. S. Manchanda and co-workers (*Indian Journal of Child Health*, vol. 7, January, 1958) reviewed 175 cases (118 in boys and 157 in girls) of bronchonasal allergy in children below the age of 14 years. Of these children 135 came from urban and 40 from rural areas. Inquiry into the housing conditions showed the atmosphere to be dusty and perhaps richly impregnated with pollens. The greatest incidence as regards the onset of symptoms was during the first five years, 23% occurring in the first year of life. The youngest age at which one of the patients presented some evidence of allergy was one week. A lactovegetarian diet was used by 115. A definite history of food allergy was obtained in only 50 cases, the common offending articles of the diet being sour preparations of milk such as curds, oily and fried foods, iced drinks, ice cream, onions, rice, chili, pulses, eggs, oranges, potatoes, and beans. One infant was highly sensitive to cow's and all dried milks and their products but not so to his mother's milk. In fact, no child was allergic to his mother's milk. History of dust allergy was present in 20 cases or 11.4%. Half the patients became worse during changes of seasons. Some developed acute attacks of bronchonasal allergy after a cold bath, cold drink, or cold breeze. In 39 patients (22.2%) pneumonia, in 18 (10.3%) pertussis, in 6 (9.1%) measles, in 2 (1.2%) smallpox, and in 1 (0.6%) diphtheria initiated or altered the course of the disease. Tonsillectomy and adenoidectomy either precipitated or aggravated the condition in nine patients.

Besides respiratory allergy, other allergic states met with in this series were urticaria in seven patients and eczema in two. A positive family history of allergy was obtained in 52 cases (29.7%). Pure nasal allergy was present in 5, bronchial allergy in 79, and combined bronchonasal allergy in 91 patients; 43 started with nasal allergy and 132 with bronchial allergy. Abnormal physical signs were found in only 98 patients and these were diffuse rhonchi in 87, prolonged expiration in 62, and crepitations in 52. Chronic bronchitis developed in 53 patients, emphysema in 46, bronchiectasis in 5, enlarged tracheobronchial lymph nodes in 4, and cor pulmonale in 1. The total leukocyte count was over 10,000 in 45. The eosinophilic count was over 4% in 116. An absolute eosinophilic count over 400 per cubic millimeter was present in 40 patients, and in 4 it was over 4,000 per cubic millimeter. Stool examination showed helminthic infestation of different types in 54 patients. Radiologic examination of the chest gave abnormal findings such as pleural thickening, enlarged glands, and pneumonitis in 22. Screening showed evidence of emphysema in 46. Skin sensitivity tests done on 19 selected patients showed a positive reaction to one or another allergen in only 11 patients.

Acute Diarrhea.—Patel and Agarwal (*Indian Journal of Child Health*, vol. 7, January, 1958) treated 52 children suffering from acute diarrhea with a combination of neomycin and sulfamethazine. None of them had received any therapy before admission; 37 were considered to be severely ill as judged by the degree of dehydration, toxemia, and general debility. The age of the patients in this series ranged between three months and seven years. All had fever. They were divided into those with (1) diarrhea alone, (2) diarrhea and vomiting, (3) involvement of the respiratory tract in addition to diarrhea, and (4) mild to severe malnutrition in addition to diarrhea. The combined treatment was given in the form of a solution during the day in four divided doses, the total daily dose being 50 mg. of neomycin and 0.6 Gm. of sulfamethazine per kilogram of body weight. Stools were examined repeatedly in the course of treatment.

The response was judged on the basis of improvement in general condition, reduction in the number and character of stools, changes in stools detected microscopically, and the rate of improvement in terms of days required. Those with diarrhea alone showed a satisfactory response within

three or four days, abnormal gross and microscopic changes being absent from the stools from the fourth day. Those with vomiting took about a day longer as the drug combination by itself did not control vomiting, and auxiliary treatment had to be given. In children with involvement of the respiratory tract, sulfamethazine was not enough to control the respiratory infection and penicillin was given. The state of malnutrition in the fourth group did not materially alter the response to therapy as far as diarrhea was concerned. Those who failed to improve with this drug combination in the vomiting and the malnourished groups, were unaffected either by increasing the dose or prolonging the therapy. The response on the whole was encouraging. No untoward effects were encountered, and there was no increase in fungus infections of the intestinal tract as a result of this therapy.

Liver Damage in Heart Failure.—P. N. Wahi and co-workers (*Indian Journal of Medical Research*, vol. 46, January, 1958) stated that prolonged congestion in the liver has been known to lead to cirrhosis and derangement of liver function. They studied clinical gradations, functional changes, and needle biopsy specimens of the liver in different stages of congestive failure. Of 61 patients studied, needle biopsy was performed on 25. The patients included those with rheumatic endocarditis, cor pulmonale, hypertensive and coronary heart disease, syphilitic heart disease, subacute bacterial endocarditis, and congenital heart disease. They were graded according to the severity of congestive failure, taking into consideration the general appearance of the patient, degree of dyspnea, venous engorgement in the neck, severity of edema, and extent of hepatomegaly. Liver function tests including the total proteins, albumin, globulin, and cephalin-cholesterol flocculation test, prothrombin time determination, bromsulfalein retention, urine urobilinogen, and serum bilirubin were performed on every patient. A 24-hour sample of urine was subjected to an electrophoretic analysis.

The extent of centrilobular hepatic necrosis was graded into three grades depending on the extent of the area involved. Central necrosis was almost invariably found in patients with any form of heart failure. The most severe form of central necrosis was seen in patients with congestive heart failure due to mitral stenosis. The authors observed histopathological changes showing the transition from the earlier centrizonal congestion to advanced cardiac fibrosis. The severity of the failure was fairly closely related to the severity of central necrosis. The latter was also closely related to the duration of the disease. Mitral stenosis was also the most common cause of cardiac fibrosis. Abnormality of liver function tests was not related closely to the severity of the disease. The albumin and globulin content, cephalin-cholesterol flocculation, and bromsulfalein excretion tended to be more abnormal in patients with advanced central necrosis. Those with severe hepatic damage gave high serum bilirubin values. Marked aminoaciduria was seen in patients with advanced congestive failure. The correlation of the clinical severity, the extent of central necrosis, and the hepatic function tests indicated that clinical judgment may be a more accurate measure of the extent of damage to the liver than the function tests alone.

Psychiatric Society.—Inaugurating the 11th annual conference of the Indian Psychiatric Society in Poona in February, Bombay's Health Minister said that a large number of mentally ill persons are in need of hospitalization in India. Such hospital accommodations fall far short of the demand and more psychiatrists appreciative of both curative and preventive treatment are also needed. In the preventive field, of about a dozen child guidance clinics in the country six are located in Bombay city and its suburbs. Bombay University is one of the two in the country offering postgraduate training in psychiatry.

Steroid Hormones and Salivary Amylase Activity.—S. N. Narayan (*Indian Journal of Medical Research*, vol. 46, January, 1958) stated that some workers investigating the steroid enzyme relationships believe that hormones exert their action by direct or indirect effect on accelerators and/or inhibitors of enzyme systems. The author determined the amylase activity of saliva from young adults before and after adding testosterone and other steroid hormones. The normal range of amylase activity in the saliva of the human subjects tested varied between 460 and 965 units, a unit of amylase activity being the amount of enzyme that under the conditions of the procedure followed in this study, in the presence of 60 mg. of starch, will hydrolyze 10 mg. of starch in 30 minutes to a stage at which no color is given with iodine. Desoxycorticosterone acetate and progesterone had a significant inhibitory effect on the amylase activity, the influence of the latter being more marked than that of the former. Testosterone propionate had only a slight inhibitory effect.

NORWAY

Public Health Legislation.—In 1957 an imposing list of legislative reforms were enacted (*Tidsskrift for den norske laegeforening*, Jan. 15, 1958). The physician who has abused his right to prescribe narcotic drugs will be dealt with by a body composed of two lawyers and two physicians. If he is convicted, he may be deprived of his right to prescribe such drugs for a period of up to five years. Judgment in such a case must be unanimous. A potential of-

V 19

fender may, however, voluntarily apply to the authorities to be relieved of his right to prescribe such drugs for a given period. In another legislative reform, control of the activities of alcoholics is extended to drug addicts. Both groups will be liable to forcible detention in an appropriate institution for up to two years. Another reform deals with the appointment of public health nurses who, working under district health officers, will have much greater scope for their activities than formerly. They will not only have educational responsibilities, but will have had to pass through a school of public health nursing. With regard to sickness benefits for insured persons, steps have been taken to prevent the mistake of letting the value of sickness benefits exceed one's earnings in good health.

Antimalarial Drugs for Asthma.—Dr. A. Engeset (*Nordisk medicin*, Dec. 5, 1957) reported on 32 patients for whose obstinate asthma condition he had given two 100-mg. tablets of quinacrine daily for three weeks and then 100 mg. daily, or two 250-mg. tablets of chloroquine daily for one week, and then 250 mg. daily. The quinacrine was apt to provoke dermatitis or psychosis, whereas the chloroquine gave rise to no serious complications. The observation period after the institution of this treatment was three months to four years. Various degrees of improvement could be claimed in 75%, and marked improvement in 53%. Improvement was noted after about three weeks, and it was usual for a relapse to occur after this treatment had been discontinued for a few months. On resuming this treatment the patients again improved. Dr. J. Böe suggested that the benefits claimed by Engeset on behalf of the antimalarial drugs reflected the personal care he devoted to his patients rather than any specific properties possessed by the drugs given. At all events no permanent cure of asthma could, in Böe's opinion, be claimed for these antimalarial drugs.

Radium Hospital.—The greatly enlarged Radium Hospital on the outskirts of Oslo was opened in 1932 with 75 patients. Another 22 beds were made available in 1941. The hospital now has beds for 310 patients (180 for general use, 90 for gynecological patients, and 40 for ambulatory patients).

Vital Statistics.—Of the 29,981 deaths that occurred in Norway in 1956 only 3% could not be accounted for, and accidents, suicides, and murders accounted among them for another 6%. Diseases of the cardiovascular system accounted for 31%, and if disease of the vessels of the central nervous system are added, then the two groups together accounted for 48% of all the deaths between the ages of 60 and 69 and for 58% between the ages of 70 and 79. Malignant disease was responsible for 19% and tuberculosis for 1.2% (which compares favorably with the 2% in the period 1951 to 1955). Syphilis was held responsible for the death of 49 men and 14 women, whooping cough for 14 deaths, measles for 12, and acute poliomyelitis for only 2. There were 1,463 deaths from pneumonia and 152 from bronchitis. It is a disquieting fact that the death rate from the cardiovascular diseases is not only high but is rising in the case of men over 50 and of women over 70.

PERU

Adrenal Hypofunction due to Paracoccidioidomycosis.—Patients with advanced lesions of paracoccidioidomycosis in the adrenals found only at autopsy have been reported, but patients with this disease showing evidences of adrenal hypofunction have been reported thus far only by Azevedo, in 1934. Dr. J. Escudero and co-workers (*Archivos peruanos de patologia y clinica*, vol. 11, January, 1957) have treated another such patient, a 55-year-old man who, after a dental extraction five years prior to admission, developed an ulcer in the labial mucosa of the lower lip. This increased in size very slowly, with periods of apparent remission. Chlortetracycline and oxytetracycline were given parenterally and orally without benefit. A biopsy specimen made at the National Institute of Neoplastic Diseases was reported to reveal Mycobacterium tuberculosis. The patient received specific therapy, made some improvement, and returned to his home. A short time later the lesion was reactivated and a cough productive of purulent sputum developed. Treatment for tuberculosis was resumed but this time there was no improvement. The patient was hospitalized in the Dos de Mayo Hospital of Lima where examination of the secretion from the labial lesion revealed Blastomyces brasiliensis but no tubercle bacilli.

Physical examination revealed a poorly nourished, slightly febrile, tachycardic patient, for whom both eating and talking were very painful. In the face, at lower lip level, an ulcer extending from the midline to the left commissure of the mouth was found. Although a roentgenogram of the chest revealed multiple pulmonary lesions, there were no physical signs in the chest. On the other hand, the patient was found to have a consistently low blood pressure averaging 80/60 mm. Hg. The erythrocyte count was 3,500,000. The sedimentation rate was increased. Cultures of sputum and feces in Sabouraud medium were positive for B. brasiliensis. Shortly after admission the patient began to complain of weakness. Based on the good responses obtained with sulfisoxazole in other patients with this disease, the authors gave this drug to the patient but, although the labial ulcer began to heal, the course was steadily downhill, and after 44 days of hospitalization he died. At autopsy

caseation of the adrenal glands, disseminated fungal lesions in both lungs and the liver, and a regressive fungal ulcer of the lower lip were found. The parenchyma of the adrenal glands was totally destroyed.

The Society of Public Welfare.—The report of the Society of Public Welfare of Lima for 1956 indicated that the number of patients treated in the six hospitals supported by this institution has steadily increased year after year. In 1956 there were 74,174 compared with 48,084 in 1945. The death rate has decreased from 6.5% in 1945 to 2.8% in 1956. A decrease was also observed in the average stay in the hospital from 40.8 days in 1945 to 24.8 days in 1956.

SWEDEN

Cancer Register.—Under the auspices of the Swedish National Health Service, a central register of cases of cancer was started in January. A similar service is already at work in the other Scandinavian countries. Three report forms have been provided. Form A is for hospital physicians, form B for pathologists' biopsy reports, and form C for postmortem findings. Although duplication is possible, experience with other cancer registers has shown that this risk can be discounted in practice. There will be no duplication when a patient moves from one hospital to another nor when relapses or metastases occur, but a new, primary growth will have a new place in the register. Provision is also made for registration of cases in which the original diagnosis is found to be mistaken. The main object of the register is to provide reliable morbidity figures, and it does not directly set out to discover survival rates after different methods of treatment for this is rather the task of the institutions concerned with the treatment of cancer. In cooperation with the Central Statistical Bureau, the register has undertaken to review all the death certificates in which cancer is mentioned.

Cerebral Palsy Survey.—Since 1952 a committee has studied the cerebral palsy problem in the city and county of Stockholm. D'Avignon and Gardeström (*Nordisk medicin*, Jan. 9, 1958) estimated that about 1.4 of every 1,000 children suffer from some form of cerebral palsy. Stockholm, with a population of over a million, has about 16,000 such patients. Of the 366 patients forming the basis of a special study, 214 were male and 152 were female. About 80% had spastic paraplegia with involvement of the pyramidal tract. The remaining 20% were made up of other forms such as athetosis, tremor-rigidity, and ataxia. It should, however, be noted that the ailment often defies classification in well-defined categories as mixed forms are common. An IQ of 75 or more was found in more than 55% and children presenting tetraplegias, ataxias, mixed forms, and tremor-rigidity were on the whole worse off in respect to their IQ than the other children. There was a history of epileptic attacks in 112 of the 366 children. The epilepsy rate was higher among the tetraplegics than among diplegics, and it was comparatively low among the athetotics. It was comparatively high among those with a mixture of athetosis and spasticity. An attempt to correlate the severity of the trauma with the IQ in evaluating the future prospects of earning a living was made with 184 patients whose IQ was 75 or more. The prognosis in this respect was moderately good in about 33%, but it was excellent in only 17%, and here the trauma was comparatively slight. The outlook for employment in the open market is poor, and the victim of cerebral palsy needs all the special training and guidance he can get before leaving school. The protected workshops needed for the victims of cerebral palsy do not yet exist in Sweden.

Tetanus.—Dr. L. Thorén (*Nordisk medicin*, Jan. 9, 1958) stated that although tetanus neonatorum has not occurred in Sweden in recent years, other forms have cropped up occasionally, with 30 to 60 cases annually between 1943 and 1954. The 47 such patients treated in Stockholm between 1946 and 1955 included 13 children who contributed 6 of the 12 deaths in this series. While there were 37 cases in the first five years of this decade, there were only 10 in the following five years, probably as a result of the use of triple (diphtheria, whooping-cough, and tetanus) immunization. The experience of a surgical hospital in Uppsala indicated that in dealing with children much depends on the skill with which they are nursed, the closest supervision being needed to detect an isolated recurrence of convulsions that may be overlooked during an illness running into weeks. Active immunization with triple vaccine should be supplemented when children begin school by a booster dose as a matter of prophylactic routine. The fear of anaphylactic shock and serum sickness in connection with passive immunization warrants a certain reserve in adopting it as a prophylactic measure, but as a therapeutic measure it should be pushed. Thorén recommended a dosage of 100,000 international units daily for four days or longer when the primary focus of the disease has eluded detection.

BCG Vaccination by Mouth.—Ström and Sternberg (*Nordisk medicin*, Jan. 9, 1958) drew attention to a lack of research on the claims made on behalf of BCG vaccination by mouth as advocated in South American countries. The authors treated guinea pigs with radioactively marked BCG vaccine to determine whether 20 mg. of the vaccine given by mouth to some animals and 2 mg. injected intracu-

taneously into others would give a 10:1 ratio of radioactivity of the serum, urine, and certain organs. They found that the rate at which radioactivity occurred in the blood was smaller after oral than after intracutaneous vaccination even when the dosage of the former was 10 times greater than that of the latter, but various other observations were less negative. It was concluded that further observations should be made.

UNITED KINGDOM

Otitis Media.—A report by the Medical Research Council reveals that many patients with otitis media are being treated by general practitioners in the patient's home (Report of a Survey by the Medical Research Council's Working Party for Research in General Practice). A survey was made by 28 physicians in various parts of the country, covering 47,000 patients, of whom 11,277 were under 15. The yearly incidence of acute otitis media in this group was 1,323, but only 14 patients, or just over 1%, were hospitalized. Children aged 2 to 14 years formed 85% of the total. The highest attack rate was for children between the ages of 3 and 6, the incidence rising to nearly 21% at the latter age. After this age there was a decline to 3% at 14 years, to 1% in young adults, and to 0.2% in those over 65. The incidence of otitis media was highest in winter and lowest in summer. More than half of the patients had had previous attacks; tonsillectomy and adenoidectomy had no effect in preventing recurrence. The mean duration of the illness was 11 days. Treatment was with sulfonamides or antibiotics, mainly penicillin, in 80% of the cases. Antibiotics were given orally in 41% and parenterally in 27%, while 27% were given sulfonamides. There were complications in only eight patients, or 0.6%. Six months after the onset 17 had persistent aural discharge, and nearly 4% of the children and 17% of older patients had some degree of deafness, which generally occurred after recurrent attacks.

Vaginal Cytology as an Index of Ovarian Activity.—Osmond-Clarke and Murray (*Brit. M. J.* 1:307, 1958) during an investigation on the possible relationship between estrogens and uterine carcinoma, also examined the value of cytology in assessing overian function. This method has the advantages of being simple, inexpensive, nontraumatic, and it does not involve the hospitalization of the patient or the use of laboratory animals. The smear is taken by inserting a glass tube with a rubber bulb attached into the posterior fornix of the vagina and aspirating secretion into the tube. The secretion is transferred to a slide and stained by Shorr's technique. The percentage of cornified squamous cells in the total cell count varies with the amount of estrogen utilized in the body. This is referred to as the cornification index. Conversely the percentage of basal cells varies with the degree of atrophy of the vaginal epithelium. The functional state of the ovaries is recorded by plotting the daily percentages of each type of cell.

Although the smear in atrophic amenorrhea consists chiefly of basal cells with an occasional squamous cell, all types of cells are present. In the hypotrophic type cells varying degrees of cornification are present, and in the hypertrophic type there is a persistently high degree of cornification. Information can be obtained in cases of infertility from a study of vaginal smears, particularly if the cycles are anovular. Some may show a cornification curve similar to that obtained in an ovulatory cycle, but without the characteristic postovular changes. Others may show evidence of a more marked abnormality. Periodic vaginal smears are of value in assessing progress in the management of the menopause by estrogens. The vaginal smear is also useful in detecting the presence or absence of estrogen in patients with uterine carcinoma.

Legal Action over Fluoridation.—Sodium fluoride has been introduced into the Andover water supply. A motion by the borough council to stop this measure was defeated by only one vote and now an "antifluoride" association has been formed in the district. This association has taken legal proceedings against the council. The writ claims that the fluoridation of a water supply is beyond the purview of the council, contrary to law, and an infringement of individual liberty. The writ further states that the council must supply natural water and not water to which fluoride has been added. It contains an injunction to restrain them from supplying fluoridated water. If this injunction is granted the council must cease supplying water containing fluoride or be collectively summoned for contempt of court.

Thalassemia Minor in an Englishwoman.—Thalassemia is a hereditary hypochromic microcytic anemia thought to be confined to the inhabitants of the Mediterranean area. A mild and symptomless form of the disease, known as thalassemia minor, occurs. Havard and co-workers (*Brit. M. J.* 1:304, 1958) observed a case in an Englishwoman. The patient, a woman of 48, was of pure English stock, her forbears having been farmers in East Anglia for many generations, without any intermarriage with foreigners. Although her mother was anemic she lived to an advanced age. The patient was referred to hospital for investigation of a hypochromic anemia refractory to iron treatment. She had two bouts of hematemesis from which she recovered, but her hemoglobin level could not be raised above 10 mg. per 100 ml. by oral or intravenous administration of iron. On examination the

only physical sign was cardiac enlargement. Hematological examinations showed an iron-resistant hypochromic microcytic anemia with target cells, basophilic stippling, reticulocytosis, and increased osmotic resistance of the red blood cells; the presence of fetal hemoglobin and an increase in a fraction of normal adult hemoglobin, designated Hb-A_2; and a normal serum iron level. A tentative diagnosis of thalassemia minor was made. This was confirmed by similar changes in the blood of two of three siblings, both of whom were asymptomatic. This is the first well-authenticated case of thalassemia in a person of British stock.

Uterine Irritability.—Dr. C. N. Smyth (*Lancet* 1:237, 1958) stated that a knowledge of the degree of irritability of the pregnant uterus is of value to the obstetrician in determining whether a patient will abort spontaneously, whether labor is imminent, or whether amniotomy or an oxytocic will induce labor. When the uterus is very irritable, labor is usually imminent. When irritability is less, a longer time will probably elapse before labor begins spontaneously. This differentiation enables patients to be kept in hospital, or to be sent home. Smyth assesses the biological irritability of the uterus by measuring the minimal dose of oxytocin required to produce a perceptible change in myometrial activity, which is recorded by a tocograph with the patient at rest in bed. The magnitude of the dose of oxytocin required specifies the degree of irritability. The dose is from 0.01 to 0.1 unit given intravenously at one-minute intervals. The oxytocic sensitivity test has useful clinical applications. When labor is induced surgically, the results of the test bear a significant relation to the interval between amniotomy and the onset of labor. They are also related to the rate of oxytocin infusion required to establish regular labor-like contractions. In normal patients near term, the test indicates how long an interval may be expected before the spontaneous onset of labor. If the test shows a constantly low uterine irritability day after day, the infant is likely to be postmature unless labor is induced. The test also provides a method of measuring the change in irritability resulting from the administration of drugs or from the application of other stimuli to the myometrium or its nerve supply.

Serum Vitamin B_{12}.—Spray and Witts (*Brit. M. J.* 1:295, 1958) assayed the serum vitamin B_{12} level in normal subjects and in patients suffering from various conditions, using a microbiological method based on the growth of Lactobacillus leichmannii. The range of values found in 123 normal subjects was 150 to 1,000 micromicrograms per milliliter (average 450). Of 94 patients with pernicious anemia in relapse, 85 gave values of 100 micromicrograms per milliliter or less, 7 gave values between 100 and 170, and 2 anomalous normal results were obtained. In patients with subacute combined degeneration of the spinal cord the level of serum vitamin B_{12} was of the same order as in those with pernicious anemia. This has proved useful in differentiating this disease from other neurological conditions. A moderate reduction in serum vitamin B_{12} is present in patients with the pernicious anemia of pregnancy although it does not reach the low levels found in patients with Addisonian pernicious anemia. Many patients develop a megaloblastic anemia as a complication of partial or total gastrectomy, small intestinal diverticulosis, blind loops left after intestinal operations, the malabsorption syndrome, dietary deficiencies, and anticonvulsant therapy. This anemia is associated with a lowered serum vitamin B_{12} level. Patients with chronic myeloid leukemia had a high serum vitamin B_{12} level. In those with chronic lymphatic leukemia normal results were obtained, and in those with acute leukemias and polycythemia both normal and high levels were found.

Serologic Diagnosis of Carcinoma.—Burrows (*Brit. M. J.* 1:368, 1958) investigated the Makari test for carcinoma and reported that it was positive in 96.7% of 301 cases of histologically proved cancer. The basis of the test is that any carcinoma will release into the circulation a substance specific to carcinoma tissue, not found in normal subjects, which is probably a molecule or part of a molecule making up the substance of the tumor itself. This substance produces a reaction with antibodies in a guinea pig that has been sensitized with carcinoma tissue. To perform the test a female virgin guinea pig is sensitized by injection with the deposit remaining after centrifuging a 20% aqueous emulsion of carcinoma tissue. A month later the uterine horns are removed, suspended in a Schultz-Dale bath, and desensitized to the normal elements in plasma; 1.5 ml. of serum from the suspected patient is added to the bath containing the immune horn and a normal control horn. If a carcinoma is present the immune but not the control horn contracts.

Many differing types of tumor, such as adenocarcinoma of the breast; adenocarcinoma, squamous carcinoma, and oat-cell carcinoma of the lung; adenocarcinoma of the rectum, colon, stomach, and prostate; hypernephroma; chorioepithelioma; and glioblastoma, including metastases, were investigated. Ten false-negatives were obtained in early squamous carcinoma of the tongue, carcinoma of the thyroid, astrocytoma, postcricoid squamous carcinoma, malignant melanoma, malignant carcinoid, adenocarcinoma of the pancreas, primary squamous carcinoma of the larynx, adenocarcinoma of the breast, and secondary adenocarcinoma (primary unknown). Of the tests of 207 patients without carcinoma, who were used as controls, 200 were negative. This also represents an accuracy of 96.7%. The seven false-positives were in patients with sim-

V 1
195

ple gastric ulcer (1), chronic granulomatous lesion of the breast (1), infarct of the brain (1), and nephrosis (4). A positive test was not obtained in patients with sarcoma or leukemia. The test was of no quantitative value, giving no indication of the size of the carcinoma, but it was sensitive to tumors as small as half an inch in diameter.

Burrows and Neill *(Brit. M. J.* 1:370, 1958) investigated the nature of the substance responsible for the Schultz-Dale test. The serum of patients with carcinoma giving a positive test was subjected to continuous paper electrophoresis, which separated an active substance preceding the albumin, which substance was thought to be a protein or polypeptide of low molecular weight. Hydrolysis and paper chromatography gave large spots due to arginine. This is in keeping with the statements that cancerous tissue contains more arginine than noncancerous tissue. It was concluded that the polypeptide found in patients with carcinoma and the peptide found in nephrosis by Dent are identical and are responsible for the false-positive reactions. The nephrosis peptide may be a breakdown product of a larger structure, produced in carcinoma from the tumor itself and in nephrosis from the accelerated catabolism known to occur. The false-positive tests produced in some cases of nephrosis could be due to an antigenic similarity between the group of polypeptides produced in this condition and the group produced in carcinoma.

Treatment of Schizophrenia with Carbutamide.—Carbutamide appears to act as a euphorizing antihallucinogen. Frost *(Brit. M. J.* 1:381, 1958) reported encouraging results in the treatment of schizophrenia with this drug. Sixty patients with schizophrenia were given 1.5 Gm. of carbutamide daily for three days, followed by a rest period of four days. This regimen was repeated for four weeks. Care was taken to see that the patients did not become hypoglycemic during treatment. Of the 60 patients, 45 were discharged recovered or relieved. Four were subsequently readmitted for a further course of carbutamide. In schizophrenia superimposed on mental deficiency or intellectual retardation the psychotic episode was cut short and restoration to home life effected. Hallucinosis sometimes disappeared in a few days, although in others it persisted. Depression often gave place to euphoria by the third week of treatment. Agitated, obsessive, and tense patients did not do so well. Carbutamide rendered paranoid schizophrenics accessible to psychotherapy in a state of clear consciousness unaffected by hallucinosis, depression, or thought blocking. One patient escaped from the hospital, found himself work, and managed to save $200 in two months. No toxic effects were observed during treatment. As glucose was given liberally throughout treatment hypoglycemic attacks were mild.

Art Among the Doctors.—The Medical Art Society held their 16th annual exhibit at Walker's Galleries in London. An artist commenting on it said that most of the exhibitors seemed to have spent their holidays abroad where there was more sunshine than in their own country. Even so, he believed that the colors were a little too bright. Two pieces of sculpture, "Fallen Horse" and "Air Borne" by Dr. G. Konstam of the West London Hospital, stole the show. The latter revealed the dynamic rhythm of an athlete's torso without overanatomizing it, an error into which even the great sculptors of the past sometimes fell. In "Depression," a study by Dr. Jakub Rostowski, a neurologist, of a mental patient with a gaunt figure and bony hands wandering over the keyboard of a piano, the emaciated subject and the facial expression suggested the most abject melancholia. Symbolism was employed in Dr. B. Brooke's "Crucifixion" with three bare crosses.

Serial Cholecystography.—Classic cholecystography gives a positive diagnosis in less than half the cases of suspected biliary tract disorder for which it is used. It may demonstrate the presence or absence of a gallbladder shadow, gallstones, subnormal concentrating power, morphologic abnormalities, and failure to contract after a fatty meal, but it will not give information on the evacuation of the gallbladder or on motor dysfunctions of the biliary tract. Rose *(Brit. M. J.* 1:360, 1958) who has demonstrated the high incidence of disturbances of motor function of the biliary tract, pointed out the necessity for a more accurate preoperative method of diagnosing such conditions. Instead of classic cholecystography, he uses serial cholecystography starting 14 hours after the ingestion of iopanoic acid, with films taken every 10 minutes after a fatty meal for 80 minutes. From the radiographs the volume of the gallbladder and the curve of the angle of erection of the gallbladder are computed. This is the angle between the long axis of the gallbladder and that of the spinal column in the lateral view. This angle is important, as any increase in it has the effect of reducing the apparent length of the gallbladder shadow in the anteroposterior view, and so must be taken into account when calculating the volume. Normally it is between 5 and 15 degrees and depends on the tone and force of contraction of the gallbladder and the resistance to its evacuation.

After the ingestion of a fatty meal the gallbladder shadow normally becomes smaller and in the anteroposterior view moves proximally and rotates externally. In the lateral view the shadow appears to rotate so that the long axis becomes more vertical and the angle of erection increases from 5 to 15 degrees. The normal volume is between 25 and 30 ml., and this may normally decrease by 70% in the first half hour after a fatty meal. Abnormally the

gallbladder may be hypokinetic or hyperkinetic and hypotonic or hypertonic. In conditions of obstruction to evacuation the curve of the angle of erection contrasts strongly with that of evacuation. The evacuation is insufficient while the angle of erection increases. If, however, the angle of erection is initially low and fails to increase during the test, the gallbladder is atonic. Of 137 patients with possible disorders of the biliary tract investigated by Rose, 40 had a normal classic cholecystogram, but serial cholecystography showed a dyskinesia which was subsequently proved at operation. The most common finding was a gallbladder that evacuated insufficiently. None of these cases would have been either diagnosed or treated correctly without the use of serial cholecystography and preoperative manometry. Rose has now abandoned classic cholecystography.

Tuberculosis in Cyprus.—The results of tuberculosis surveys in Cyprus were reported on by Constantinides (*Tubercle* 39:59, 1958). The country does not lack medical facilities, as there is a physician to every 1,400 persons. There are five chest clinics, one in each of the principal towns, attached to the district hospitals, whose facilities they use. They give BCG vaccinations to persons exposed to known risk of infection, contacts, and immigrants. There are two tuberculosis sanatoriums, and recently a mobile mass radiography unit was activated. A tuberculosis survey of 4,500 children aged 6 to 12, using the Moro tuberculin test, revealed positive reactors in only 8.3%. A recent WHO survey showed that 90% of the children aged 15 were negative to tuberculin. The first measure in the campaign against tuberculosis was curative, but now the preventive aspect is being considered. It is planned to extend BCG vaccination, to undertake serial tuberculin testing of all children under 12 years, to treat infected children by means of chemotherapy, even for minimal lesions, and to expand the mass miniature radiography service.

Epidemiologic Research.—Students at the London School of Hygiene and Tropical Medicine are now given a course in epidemiologic research. Last year one group investigated the habits and health of London's cab drivers, in whom they found a fairly low rate of sickness and absenteeism. These men are noted for their strongly independent character. It was found, however, that some of the men suffered from chronic respiratory conditions, psychosomatic diseases, and hemorrhoids. Another group investigated the possible harmful effects of commuting on health. The wear and tear of long-distance commuting, often involving several transfers, is commonly thought to undermine the health, but the students found no statistical correlation between the distance traveled to work and absenteeism. A third group, however, did report that young persons traveling daily from Dagenham to London showed slightly more absenteeism than would be normally expected. The students also studied the complaint of unhygienic food handling. They examined booklets, leaflets, film strips, and posters available to the public and to food handlers but were not impressed. They considered that they lacked the punch of similar transatlantic material. More use of radio and television propaganda was suggested. Although there were films and film strips on the correct handling of food, there was nothing on the incorrect handling. The students made a short film of their own on this.

A special study was made of chronic bronchitis, which is still a major problem in Great Britain. The comparison of a group of middle-aged men with chronic bronchitis and control subjects in the same age group revealed that overcrowding (particularly in childhood), poverty and low social class of the patient's parents, living in towns, and smoking 20 or more cigarettes daily appear to be associated with the disease. Many students were impressed with the seriousness of chronic bronchitis in middle-aged men, the extent of domiciliary nursing care needed at home, and the search by patients for costly panaceas.

Rise in National Health Service Contributions.—Owing to mounting costs the weekly contributions to the National Health Service are to be raised next July by 7 cents for men, 4.5 cents for women, and 2 cents for juveniles. The employer will pay an extra 2 cents. Although small these increases will bring in another $67,500,000. Even so the personal contributions will only pay for just under 20% of the total cost of the health service. It is possible that if contributions are increased in the future they will be based on income rather than on a flat rate for the whole of the population. At present millionaires pay the same contribution as laborers.

"Head Hunting" by Physicians.—The General Practice Reform Association, representing young physicians, has submitted a memorandum to the Royal Commission on Doctors' and Dentists' Remuneration. The association refers to the need for general practitioners to collect as many patients as possible, which it refers to as "head hunting," to secure adequate remuneration. This is because the present system of payment is based on the number of patients registered with a physician. Up to 3,500 are allowed, or 5,500 if the physician employs an assistant. The association claims that an established practitioner will take all the legitimate steps he can to keep out a newcomer. There are thus two groups of physicians, those who have large lists of patients and thus earn an amount sufficient for their needs, but at the expense of overwork and rushed work, and those who are underemployed and underpaid

because they have small lists. Many physicians with large lists would prefer to have smaller ones but cannot afford to do so. As a result their standards tend to fall, and the public suffers. To remedy this defect the association suggests an immediate reduction in the maximum size of patient lists in the national health service to 3,000 and reduction eventually to 2,000 after 10 years. This would necessitate raising the present capitation fee from $2.46 to $3.65 per patient per year.

British Broadcasting Corporation Criticized.—A BBC broadcast of a discussion on artificial insemination was criticized in an editorial in the *British Medical Journal*, which had previously attacked the BBC's choice of medical programs. It accused the BBC of "pandering to the prevalent interest in the morbid" by a series of telecasts on operations under the title "Your Life in Their Hands." It stated that the BBC is determined to make people's flesh creep by showing details of operations. In a program called "The Unknown Seed," two women and two physicians took part in a discussion on artificial insemination. To ensure privacy the recording was made in the consulting rooms of a London specialist. The *British Medical Journal* stated that such broadcasts fortify the public taste for the morbid and sensational.

CORRESPONDENCE

MUNCHAUSEN SAGA

To the Editor:—The Munchausen saga of Leo Lamphere seems to run a course for not only the edification of the medical journals but the newspapers as well. The last sentence of Dr. Chapman's letter in THE JOURNAL, Feb. 15, 1958, page 823, ends with "permanent custodial care in a mental hospital." The Feb. 18 Cincinnati *Post* carried the following headlined story: "Law finally catches fantastic hospital bum." It tells how he stumbled into the police station in Crawfordsville, Ind., spitting blood. The officers rushed him to the hospital where his identity was recognized 24 hours later. He was then jailed—pending commitment to a state mental institution at Westville, Ind.

On Jan. 20, this same man staggered into the emergency room of the St. Elizabeth Hospital, in Covington, at 3 a. m. He told the intern that he was on a bus on his way to New York and coughed up blood an hour earlier. He had chest pain that radiated to his left shoulder. He gave a history of thrombophlebitis of the left thigh. He was admitted to the medical service. Meperidine hydrochloride was given, which seemed to answer his purpose. The next day, along with routine laboratory work, an electrocardiogram was taken and was normal. Shortly after the doctor on service came in to see him, he was recognized and was questioned accordingly. He denied he was the man suspected and shortly asked if it was all right for him to continue his trip. He was encouraged to do so, but he did not leave until 8:55 p. m.

Later that night, across the Ohio River, at the Jewish Hospital, he staggered into the emergency room and announced to the night supervisor that he had a pulmonary infarct and so told the resident in medicine when he was called to see him. As he was talking to the resident he asked to be excused and went to the men's room. When he came back he spat out a mouthful of blood all over himself and the floor. He was told to go across the street to the Cincinnati General Hospital since a bed was not available at the Jewish Hospital. He wanted to wipe up the floor before he left. He never arrived at the hospital across the street. Interestingly enough, at the next medical conference the medical resident reported the incident, and a grand time was had by all discussing the Munchausen syndrome. By an interesting coincidence the medical resident who was present at Iowa City, and who was one of two doctors who had had him committed to a mental institution in Iowa, was in the audience. He related how the University Hospital was divided into two camps about the patient, who was finally committed. However, he escaped two weeks later!

I have a good hunch that he will escape again and be on the loose for other letters to come.

CHARLES BARON, M.D.
209 W. 34th St.
Covington, Ky.

MEDIEVAL MEDICAL MANUSCRIPTS

To the Editor:—I am card-listing medieval medical manuscripts (prior to 1600 A.D.) in the collections owned by physicians, other individuals, and public institutions in the United States and Canada. I would appreciate information as to any such manuscripts that are not already listed in the De Ricci Census of Medieval and Renaissance Manuscripts in United States and Canada.

L. C. MACKINNEY, Ph.D.
Department of History
University of North Carolina
Chapel Hill, N. C.

MISCELLANY

STAPHYLOCOCCIC INFECTIONS IN THE NEWBORN

The headquarters of the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill., has submitted the following statement as of February, 1958:

SPECIAL REPORT OF THE COMMITTEE ON FETUS AND NEWBORN

Prepared with the assistance of the Committee on the Control of Infectious Diseases and Special Consultant
Warren E. Wheeler, M.D.

STAPHYLOCOCCAL INFECTIONS IN THE NEWBORN

In the past few years there has been increasing awareness of the problem of infections due to antibiotic-resistant staphylococci. Recent studies have stressed certain aspects which indicate particular hazard for infants in newborn nurseries:

1. While there is no striking increase in staphylococcal infections in the public at large, there is an appreciable incidence of these infections in hospitalized patients.

2. There is a high carrier rate of antibiotic-resistant strains of staphylococcus in hospital personnel and in long-term patients.

3. Certain strains of staphylococcus appear to become established in a particular hospital, and different hospitals may be repositories for different strains.

4. The development of resistant strains from an originally sensitive one in a case of infection is not a very large problem. The major problem is in cross-infections by resistant strains already existent in the hospital.

5. The chance for development of staphylococcal infection in a hospital is greatly increased in individuals who have decreased resistance to infection in general.

It is apparent from the above that infants in newborn nurseries are in particular jeopardy. Several epidemics of staphylococcal infections in newborn nurseries have already been reported. In these a specific type of staphylococcus is usually found to predominate in the cultures from lesions and is usually present in high incidence in the noses of babies, nurses, and attendants and may be found in the air, dust, or on furniture of the nurseries. Studies have indicated that these infections *do not* come from the mothers but from the hospital environment.

Of great significance is the fact that newborn infants may not develop their infections for several days to weeks after they have returned home. This demands that close surveillance of newborn infants be continued after discharge from the hospital.

Certain recommendations seem justified at the present time:

1. There should be strict adherence to the principles of aseptic and antiseptic technic as set forth in the "Standards and Recommendations for Hospital Care of Newborn Infants."

2. All hospitals should establish forthwith a Committee on Control of Cross Infections with one person as the responsible individual. In maternity hospitals and children's hospitals this person would logically be a pediatrician.

3. The Committee should be empowered to make and enforce recommendations for the prevention, investigation, and control of staphylococcal and any other type of infection in the hospital population.

4. The Committee in each hospital should arrange for culturing the disease-producing strains and for identifying the "hot" strains in the affected infants and in the contacts and environment of the hospital. Specific classification of the staphylococci will require determination of antibiotic sensitivity and phage typing, and arrangement with local, state, or federal health agencies may be necessary.

5. Every visiting physician should be circularized as to the importance of informing the Committee at once of the occurrence of any infection in a newborn or its mother *after* discharge from the hospital. (In one hospital a postcard technic for ward patients is in use, wherein the mothers are instructed to report back one week following discharge concerning the condition of the baby, particularly as regards skin infections, failure to gain, or other unusual symptoms.)

6. In the case of an outbreak of staphylococcal infection in a nursery, culturing of the lesions of affected babies, the noses of all other babies and all staff personnel should be carried out. The specific measures for control of the epidemic should be worked out by the Committee in conjunction with local public health authorities.

7. Distribution of information concerning staphylococcal infections in the newborn would be expedited if information about outbreaks were reported to the Committee on Fetus and Newborn and the Committee on Control of Infectious Diseases of the American Academy of Pediatrics.

8. It is recommended that all staphylococcal infections in the newborn period be made reportable.

Irving Schulman, M.D., Chairman
Fred H. Allen Jr., M.D.
Charles D. Cook, M.D.
Eugene H. Crawley, M.D.
Bruce D. Graham, M.D.
Paul A. Harper, M.D.
David Y. Hsia, M.D.
Benjamin M. Kagan, M.D.
Robert M. Keagy, M.D.
Edith L. Potter, M.D.
William A. Silverman, M.D.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Serum Glutamic Oxalacetic Transaminase in Myocardial Infarction: Diagnostic and Prognostic Value. P. F. Hansen and T. Laursen. Danish M. Bull. 4:248-251 (Dec.) 1957 (In English) [Copenhagen].

Two or more serum glutamic oxalacetic transaminase (SGO-T) determinations were made in 147 patients admitted with the diagnosis of certain or suspected myocardial infarction. Increased SGO-T values were found in 84 of the 89 patients with certain myocardial infarction. Twenty-three of the 84 patients died; autopsy in 21 cases showed recent infarction in all. The values were increased in from one-third to one-half of the clinically doubtful cases. SGO-T determinations in clinically and electrocardiographically doubtful cases are regarded as of considerable discriminatory diagnostic value. This also holds for patients suspected of having myocardial infarction but for whom the diagnosis was clinically excluded. The diagnostic value of the SGO-T determinations lies in the possibility of early diagnosis. The early mortality shows good correlation with the height of the SGO-T determination, but the prognosis in clinically certain cases does not seem to be better evaluated by this test alone than by the criteria used hitherto, such as high fever and leukocytosis.

Auricular Infarction. J. M. Kaufman, G. Timmis and J. Forest. J. Michigan M. Soc. 57:59-62 (Jan.) 1958 [St. Paul].

The authors found only two reports in which the correct diagnosis of infarction of the atrium was made during life. They present a report on a third patient in whom acute atrial infarction was correctly diagnosed before the patient died and was confirmed at autopsy. The patient was a 62-year-old man who was admitted to Harper Hospital on July 27, 1956, complaining of a sudden onset of nausea and vomiting 3 hours prior to admission, followed by pain in the anterior part of the left side of the chest, which radiated into the left shoulder and arm. The pain persisted in spite of therapy with glyceryl trinitrate (nitroglycerin). On admission, however, the patient obtained considerable relief from the administration of morphine and atropine. He claimed to have had 3 similar episodes 8 years ago but apparently had not been seen by a physician at that time. The admission electrocardiogram was interpreted as follows: complete heart block, acute auricular myocardial infarction, and acute posterior myocardial infarction. On the evening of admission there was conversion to a normal sinus rhythm. Electrocardiograms taken on July 28 and July 29 showed progressive changes of acute posterior myocardial infarction in the presence of a normal sinus rhythm and occasional ventricular premature beats. On July 30 a second-degree heart block and Wenckebach's phenomenon with trigeminy were observed. At the end of the tracing, beginning auricular fibrillation was recorded. By July 31 the rhythm was again found to be basically regular with frequent supraventricular extrasystoles and a wandering pacemaker. Although the patient's hospital course had been relatively uneventful, on the sixth hospital day he suddenly cried out in pain and was found to be in shock, pulseless, and cyanotic. A few minutes later he was pronounced dead.

Involvement of the atrial myocardium by infarction was generally thought to be exceedingly uncommon until 1942, when Cushing and his associates reported 31 instances of it in a series of 182 cases of myocardial infarction. The incidence of atrial infarction (either as an isolated finding or as a concomitant with ventricular infarction) varies, according to several larger series reported, from less than 1% to 24.5%. The average seems to be in the vicinity of Cushing's reported 17%. Since there is no suggestive symptom complex, the diagnosis of atrial infarction must depend on electrocardiographic evidence alone. This involves primarily the detection of various arrythmias, which are usually transient and rapidly changing. The variations in the atrial mechanism include fibrillation, flutter, extrasystoles, tachycardia, sinus arrest, wandering pacemaker, and atrioventricular nodal rhythm. Disturbances in conduction are not uncommon. Any degree of heart block, including Wenckebach's phenomenon, may be detected. Most investigators agree that deviation of the PTa segment, with or without a changing contour in the P and PTa

The place of publication of the periodicals appears in brackets preceding each abstract.

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waves, is also indicative of atrial infarction. The P and PTa waves may be broadened, slurred, or notched, or a change in amplitude may be detected.

Pulseless Disease, Takayashus Syndrome: Arcus-Aortae Syndrome. P. Ollendorf. Nord. med. **58:** 1739-1741 (Nov. 7) 1957 (In Danish) [Stockholm].

To date, 99 cases of pulseless disease have been published, 14 of them from Scandinavia. The disease occurs predominantly in young women. It is a chronic arteritis which affects especially the large arteries of the aortic arch, causing a gradual closing and resulting ischemia of the upper extremities, head, and neck. In some cases the disease also attacks the arteries to the lower extremities. The etiology is unknown. The prognosis is unfavorable. The disease is slowly progressive. Duration of life is usually from 5 to 10 years after recognition of the disease; survival of over 25 years has been recorded. In the case described, which is the 100th in the literature, a woman, aged 41 years, developed hemiparesis 4 years earlier. She now presents signs of vascular closure and consequent ischemia, atrophy of the jaws with loss of teeth, stenosis bruit over the carotids and weak or absent pulsation in the arteries of the head and arms, weak or absent pulsation in the femoral arteries, intermittent claudication in both lower extremities, and violent attacks of precordial pain, with changes in the electrocardiogram pointing to ischemia of the myocardium. Reduced blood supply to the lower extremities has not previously been described in women with Takayashu's syndrome. Defective blood supply to the heart in this disease has been seen only once before.

BCG Vaccination in a Tuberculosis Prevention Program. S. R. Rosenthal. Minnesota Med. **41:**8-12 (Jan.) 1958 [St. Paul].

A healed primary tuberculous infection in human beings, in the lung or elsewhere, confers an increased resistance against virulent reinfection. This is attested by a decreased incidence of disease, a greater localization, and a better prognosis. Paradoxically, however, even in healed infection, the possibility that viable organisms may produce active disease at a later date is present, since in many instances they may remain viable in the body. It is for this reason that artificial immunization with an organism such as BCG, which can be controlled, would be highly desirable when its potentialities as a vaccine, though not as great, approach those of the virulent organisms.

Recent clinical studies with BCG in the dried form, which is produced by Research Foundation and the University of Illinois and is well standardized before distribution, showed that it is a highly effective vaccine for the prevention of tuberculosis. It should never be considered as a substitute for the time-honored and time-tested principles of tuberculosis control but as an adjunct to these methods. BCG vaccination is recommended for infants and children in areas of high incidence and for those persons who will be unavoidably exposed to tuberculosis, such as medical and nursing students, members of tuberculous households, and persons admitted to penal and mental institutions. These recommendations have been made by the American Trudeau Society, which is the medical branch of the National Tuberculosis Association, and the U. S. Public Health Service and have been recognized by the Council on Drugs of the American Medical Association.

Occurrence of Adenovirus Infections in Civilian Populations. W. S. Jordan Jr. A. M. A. Arch. Int. Med. **101:**54-59 (Jan.) 1958 [Chicago].

This paper reviews the data relative to the frequency of occurrence of adenovirus infections in civilian populations. In marked contrast to their behavior in recruit populations, the adenoviruses have been related etiologically to but a fraction of the respiratory illnesses experienced by different segments of the civilian population. Infections due to type 4 and type 7 adenoviruses, particularly type 4, have been and are infrequent in civilians. Type 3 adenovirus has most often been responsible for epidemics in civilian groups.

Serologic studies indicate that many persons have been infected with adenoviruses. By the age of 5 years, 50% of children have been infected with at least one type. Infections continue to occur throughout adolescence, and nearly all adults have antibodies to at least one type of virus. During a given respiratory season, however, only approximately 4% of the civilian population is infected with an adenovirus, and these agents account for but from 0.5% to 3% of the respiratory illnesses. It is estimated that use of a completely effective adenovirus vaccine would result in only a 6% reduction in the number of common respiratory illnesses experienced by an average child during the first 10 years of life. Present evidence does not warrant adenovirus immunization of such civilian groups as families or university student populations.

Perforation of Peptic Ulcer Following Paracentesis in Patients with Cirrhosis. S. S. Koide, E. C. Texter Jr. and C. W. Borden. Am. J. Digest. Dis. **3:**24-37 (Jan.) 1958 [New York].

During a 32-month period, from January, 1954, through August, 1956, 252 consecutive patients were admitted to the Veterans Administration Research Hospital. These patients had adequate clinical, biochemical, or morphologic evidence for the diagnosis of cirrhosis. Thirteen of them had a

peptic ulcer, an incidence of 5.2%. The incidence of peptic ulcer is higher in patients with cirrhosis than in the general hospital population, and this incidence increases in relation to the severity of the cirrhosis. Four of the 13 patients had ascites. Paracentesis was carried out in 2 of these patients, and in each instance a perforation developed after the paracentesis. A third patient who had minimal ascites also died of a perforated duodenal ulcer. The fourth patient with ascites died of a bleeding ulcer.

The authors suggest that a sudden decrease in intra-abdominal pressure secondary to the removal of the ascites would greatly increase the pressure difference between the lumen of the intestine and the abdomen. This pressure change would be ample to perforate the thin base of an ulcerative lesion. Successful management of this emergency is based on the diagnostic consideration of perforation in a patient in whom shock or abdominal pain develops shortly after paracentesis. Diagnostic aids include performance of a diagnostic tap and roentgenologic examination of the abdomen for free air. If the diagnosis can be made, surgical intervention is indicated, since the mortality rate is certain to be less after surgical treatment than after expectant medical care.

Hypernephroma from Internal Medical and Surgical Viewpoint. G. Jönsson and E. Truedsson. Nord. med. **58**:1622-1625 (Oct. 24) 1957 (In Swedish) [Stockholm].

From 1940 to 1954, 175 patients with nephroma were admitted in Lund—114 in the surgical department and 61 in the medical department. The classic triad of symptoms in nephroma consists of hematuria, pain, and palpable tumor. Not all these symptoms were present in every case. Diagnosis can be difficult. It is most easily made when hematuria is the initial symptom. Macroscopic hematuria calls for a complete urologic examination, even though the hematuria occurs only once. General symptoms, not easily interpreted, in the form of fatigue, poor appetite, and emaciation, together with increased sedimentation rate and fever, characterized the medical cases. Demonstrable metastases when diagnosis was made were found in one-half of the medical cases and in one-fourth of the surgical cases. Urography in 104 of the surgical cases revealed renal changes in 102 cases; in 1 case renal angiography revealed a nephroma of walnut size; and in 1 case repeated urography showed a nephroma. In the medical cases the diffuse clinical symptoms did not motivate intravenous urography till late. The more advanced stage of the disease in the medical cases is reflected in the prognosis: only one-eighth of the medical patients survived after 5 years as against one-third of the surgical patients. The prognosis might be improved if patients with macroscopic hematuria were given at once a complete urologic examination and if in the patients with diffuse symptoms the possibility of nephroma were considered. At present the prognosis in nephroma is poor.

Further Clinical and Investigative Uses of Liver Biopsy: An Analysis of Five Hundred Twenty-Seven Biopsies. K. L. Stuart, G. Bras, S. J. Patrick and J. C. Waterlow. A. M. A. Arch. Int. Med. **101**: 67-83 (Jan.) 1958 [Chicago].

At the University College Hospital of the West Indies the authors performed 527 biopsies, specimens of liver tissue being taken from 330 patients with the following conditions: kwashiorkor, marasmus, veno-occlusive disease of the liver, vomiting sickness, diabetes mellitus, various neuropathies, nephrosis, sickle-cell anemia, and unexplained hepatomegaly, splenomegaly, jaundice, pyrexia, and anemia. The tissue obtained for biopsy was examined histologically in all cases, and in some cases chemical examination of the liver tissue was also performed. The chemical studies included nucleic acids and protein, water and fat content, and glycogen estimations. In the patients with malnutrition it was shown (1) that the degree of fatty infiltration is no indication of the severity or probable outcome of the disease, (2) that hepatic protein depletion is severe in these patients but that its degree cannot be quantitatively correlated with the clinical picture or prognosis, and (3) that fatty infiltration does not apparently interfere with the ability of the liver to store glycogen. Occlusion of the smaller and medium-sized branches of the hepatic veins is responsible for the hepatomegaly and ascites found clinically in veno-occlusive disease. The prognosis of veno-occlusive disease is linked with the severity of the associated hepatocellular damage. Serial biopsies made it possible to define more accurately the natural history of this disease. In patients who recover, the histological appearances of the liver return to normal. When the disease advances to the chronic stage, a progressive nonportal cirrhosis is found in biopsy specimens.

The histological liver changes in diabetes are minimal and cannot be correlated with the response to treatment, clinical hepatomegaly, or alteration of liver-function tests. The hypoglycemia of vomiting sickness is associated with severe depletion of hepatic glycogen, which is rapidly restored by successful glucose therapy. There is a high incidence of fibrosis of the liver in patients with sickle-cell anemia, and a possible etiological relationship is suggested. Because of the frequently mixed na-

ture of hepatic cirrhosis in the tropics and the variability of the clinical syndromes presented, biopsy of liver tissue is a useful and often essential tool for establishing a correct diagnosis. Its advantages in unexplained hepatomegaly, jaundice, and splenomegaly have been demonstrated. It is also pointed out that biopsy of liver tissue often makes it necessary to alter an apparently firmly established clinical diagnosis. The simultaneous histopathological and chemical examination of portions of the tissue obtained at biopsy has advantages.

Alcohol Pain in Hodgkin's Disease. J. Kühböck and E. E. Reimer. Wien. Ztschr. inn. Med. **38**:454-457 (Nov.) 1957 (In German) [Vienna].

The symptomatology of Hodgkin's disease varies from patient to patient, the symptoms being largely determined by the organ that is involved, but there are also symptoms which cannot be explained on this basis, and "alcohol pain" is one of these. It has been observed even after the consumption of minute quantities of alcohol, such as that in alcohol-filled bonbons. Opinions differ as to the incidence of this pain. The authors studied this symptom in 30 patients with Hodgkin's disease who were admitted to their clinic during the course of the last year. Each patient was first asked whether he had experienced pain after taking alcohol. Then the test was made, the alcohol being given either by mouth or intravenously. In evaluating the results, care was taken to differentiate between local and general sensations, since only local pain reactions can be regarded as a positive outcome of the alcohol test.

Inquiry about pain reactions to the intake of alcohol revealed only 1 woman who stated that she had had pain in the right arm and leg a few minutes after drinking a glass of beer. The intravenous alcohol tolerance test gave a negative result in this patient. Three other patients gave a positive reaction to the intravenous alcohol tolerance test. The oral alcohol test was positive in 1 patient, who experienced severe pains in 1 leg, presumably caused by retroperitoneal lymphomas. These pains occurred 45 minutes after the oral intake of the alcohol. The intravenous alcohol test was negative in this patient. Thus, the alcohol pain was revealed either by history or by test in 5 of the 30 patients (16.6%). The authors feel that, if the alcohol test is positive, it represents definite proof of Hodgkin's disease, but a negative outcome does not speak against this diagnosis. The tests should be made by mouth as well as by intravenous injection, because when one is negative the other may be positive. The positive test helps to differentiate Hodgkin's disease from other diseases of the lymph nodes, such as lymphomatic leukemia and tuberculosis of the lymph nodes.

SURGERY

Pulmonary Sequestration: A Review of the English Literature with a Report of Four Cases. A. B. Eaker, J. L. Hannon and S. W. French III. Am. J. Surg. **95**:31-39 (Jan.) 1958 [New York].

A review of the English literature revealed that in the past 10 years many case reports of a congenital syndrome resulting from a disassociated mass of nonfunctioning pulmonary tissue associated with an abnormal pulmonary artery have been published. The syndrome has now become accepted as a clinical entity by surgeons and pathologists; it is referred to as "pulmonary sequestration" and is further divided into extralobar and intralobar types. Extralobar sequestration refers to complete ectopia or an extra lobe, occurring either above or below the diaphragm. Intralobar sequestration, over 100 cases of which were collected from the literature, although functionally dissociated is incorporated within the visceral pleura of the affected lobe. This type results in the symptoms and physiological aberrations which have made pulmonary sequestration a clinical entity and a surgical problem. Most of the authors concur with Pryce in the concept of the origin of the bronchopulmonary mass and its correlation with the anomalous artery from the aorta. The age of onset of symptoms is usually in the first or second decade, and surgical intervention is usually performed by the age of 30 years. Most patients have a history of symptoms referable to chronic recurring respiratory infection, and erroneous diagnosis of bronchiectasis, pneumonitis, pneumonia, empyema, lung abscess, and congenital disease have been made. There may be intermittent cough, chest pain, fever, chills, and hemoptysis. The chest roentgenogram is the principle measure in the diagnosis of intralobar pulmonary sequestration. Surgical excision is the treatment of choice.

The author reports 4 cases of the intralobar type of pulmonary sequestration in a 6-year-old girl, a 25-year-old woman, and 2 men aged 24 and 39 years respectively. A left thoracotomy was performed, and resection of the sequestered cystic segment was carried out in the 2 female patients and in the younger men. In the other man, multiple thoracotomies were performed for excision of congenital cystic areas. There were recurrent symptoms from infection, and ultimately lobectomy was necessary. Unless there is a question of minimum pulmonary reserve, lobectomy rather than partial resection should be performed on all patients with intralobar pulmonary sequestration. Certain cases diagnosed early, before infection has developed, may lend themselves to a clean segmental resection of the sequestrated portion; the operative morbidity and mortality should then not be much more than that of exploratory thoracotomy. More careful attention should be given preoperatively to

the symptoms and roentgenological findings which are characteristic of intralobar pulmonary sequestration. At surgical intervention, special attention should be given to dissection in the vicinity of the inferior pulmonary ligament and the diaphragmatic surface of the lower lobe, with a view to identification of aberrant vessels arising from the aorta. These should be carefully ligated before cutting.

The incidence of intralobar pulmonary sequestration has not become established. It is more frequent than was previously thought. Being a developmental anomaly, it may be found in association with other congenital aberrations of the diaphragm. This gives the condition additional importance with the increasing trend of repairing diaphragmatic (hiatal) hernia from above. Resection of the sequestrated portion of the lung can be accomplished in conjunction with repair of the diaphragmatic hernia.

The Nature and Treatment of the Postcommissurotomy Hyponatremic Syndrome. G. J. D'Angelo, H. V. Murdaugh Jr. and W. C. Sealy. Surg. Gynec. & Obst. **106**:87-91 (Jan.) 1958 [Chicago].

After the introduction of surgical corrective procedures for mitral stenosis, there evolved 2 clinical patterns which have been referred to as the "postcommissurotomy syndrome." One syndrome is characterized by chest pain and recrudescence of symptoms; the other is characterized by oliguria, water retention, hyponatremia, and hypochloremia. The authors discuss the second, which is referred to as the "postcommissurotomy hyponatremic syndrome." They observed this syndrome in 5 of 21 patients who underwent commissurotomy. For control purposes, complete data were obtained on 8 consecutive postcommissurotomy subjects. It could not be predicted preoperatively which patient would develop this syndrome after cardiac surgery. In general, however, the occurrence of hyponatremia appeared to correlate with the complexity of the patient's course prior to surgery. In those patients who developed the syndrome, the serum sodium concentration and the plasma osmolarity decreased appreciably. There was a decrease of 7 to 20 mEq. per liter in the serum sodium and a drop of 6 to 20 milliosmols (mOsm.) per liter in the plasma osmolarity. The serum potassium rose in 4 of the 5 patients from a preoperative mean of 4.5 mEq. per liter to a postoperative mean of 5.1 mEq. per liter. In the control series the serum sodium and serum potassium levels and plasma osmolarity remained essentially unchanged after surgery.

Treatment by the administration of absolute alcohol (20 to 50 ml.) resulted in a marked increase in the urinary output with, a return of the plasma osmolarity and serum sodium, serum chloride, and serum potassium levels to normal. Studies of urinary electrolyte excretion during the phase of increased urinary output suggest a true water diuresis with conservation of sodium and potassium. The possible mechanism of the phenomenon is discussed. These studies indicate that alcohol is an effective therapeutic tool in the management of the postcommissurotomy hyponatremic syndrome. The importance of fluid restriction after mitral commissurotomy is stressed.

Hiatus Hernia, Peptic Esophagitis, and Peptic Ulcer. G. M. Carver Jr. Surg. Gynec. & Obst. **106**:77-81 (Jan.) 1958 [Chicago].

Of 150 patients with peptic esophagitis studied during the past 20 years, 120 had an associated hiatus hernia and 30 had hiatus hernia, esophagitis, and duodenal or gastric ulcer. The mean age for the group was 56 years, the oldest patient being 71 years and the youngest 31 years of age. There were 23 men and 7 women. Medical management of patients with this triad was satisfactory in only 4 of 30 cases. Results of subtotal gastric resection without repair of hiatus hernia were not rewarding in 5 patients. In 7 patients peptic esophageal stenosis developed, requiring resection in 4 because of unsuccessful and prolonged attempts at medical management. Subtotal gastric resection with transabdominal anatomic repair of the hiatus hernia is advisable early in the course of the disease to prevent esophageal stricture formation. Fifteen patients so treated had excellent postoperative results without recurrence of the hiatus hernia. The anatomic technique of transabdominal repair of esophageal hiatus hernia is described, with emphasis on the preservation of the phrenoesophageal ligament and anatomic closure of the esophageal hiatus.

Subtotal Gastric Resection for Benign Peptic Ulcer: A Follow-up Study of Three Hundred Fifty-Three Patients. N. Hastings, J. A. Halsted, E. R. Woodward and others. A. M. A. Arch. Surg. **76**:74-80 (Jan.) 1958 [Chicago].

In 1950 a program was established at the Wadsworth Hospital, Veterans' Administration Center, Los Angeles, Calif., to investigate the results of various methods of treatment for peptic ulcer. The present report is a study of patients who were treated by a subtotal gastric resection from 1947 through 1954. During this 8-year period, more than 6,000 patients were discharged with a final diagnosis of a benign peptic ulcer. In studying the long-term results of subtotal gastric resection for benign peptic ulcer, the 1,048 patients who had this operation during the 8-year period were requested to report for follow-up examination, provided the operation had been performed at least 1 year prior to such examination. Three hundred fifty-three patients, or 34% of those who had this type of surgical procedure, were seen. The dura-

tion of follow-up varied from 1 to 7 years and averaged 2.5 years. All patients were interviewed by a medical-surgical team, with liberal use of x-ray and laboratory aids. Of the patients with duodenal ulcer, 68% had a satisfactory result (excellent or good), and 23% had an unsatisfactory result (fair or poor); in 9% recurrent ulceration developed (failure). In patients with benign gastric ulcer, the results were satisfactory in 78% and unsatisfactory in 21%, and 1% had recurrent ulceration.

The patients' opinions of the operative result frequently failed to correlate with the physicians' evaluations. Malnutrition was a frequent cause of an unsatisfactory clinical result, 55% of such patients having excessive weight loss. Dietetic study indicated that the weight loss was due to a greatly diminished daily caloric intake. The difference in marginal ulcer rate accounted almost entirely for the better results obtained in patients with gastric ulcer. While the recurrence rate of 9% in the duodenal ulcer group seems high, several reports of other investigators cite similar results. It is concluded that the marginal ulcer rate after the usual subtotal gastrectomy for duodenal ulcer has been performed is higher than has generally been recognized.

Epidural Hematoma. M. Tengesdal. Nord. med. 58:1569-1573 (Oct. 17) 1957 (In Norwegian) [Stockholm].

In the diagnosis of epidural hematoma the occurrence of a well-marked lucid interval is significant. A short lucid interval usually means that the disease runs a rapid course. In the 11 cases reported, the lucid interval varied from ½ hour to 9 days. The 6 patients with lucid interval of an hour or less all died; 3 died immediately after admission, and in the other 3, with symptoms of decerebrate rigidity, operation was of no avail. The 5 surviving patients had a longer lucid interval. The possibility of epidural hematoma cannot be excluded because there is no lucid interval. Findings at autopsy show that epidural hematoma not infrequently occurs together with other grave intracranial injuries. In this group the general symptoms of nausea, vomiting, headache, bradycardia, and changes in blood pressure were of little value in diagnosis. The initial brief loss of consciousness in epidural hematoma is probably due to brain concussion. Loss of consciousness after a transitory lucid interval is an early sign. Semicoma and coma are danger signs. Five of the 6 patients who died were in coma, and 1 patient was in semicoma. Of the 5 who recovered, 1 patient was somnolent, 1 was in semicoma, and 4 were soporous. There were symptoms from the oculomotor nerve in all cases. Symptoms of disease of the pyramidal tracts come early and often and are ascribed partly to the hematoma, partly to herniation of the temporal lobe. Total areflexia and decerebrate rigidity are terminal signs. The high mortality in epidural hematoma can be reduced by earlier diagnosis and treatment. In case of suspected hematoma the patient should be admitted at once to the nearest hospital, and if there are grave signs of herniation, trepanation should be done there. If hemostasis gives trouble, the patient can after careful tamponade be sent to a special division. Preliminary decompression considerably improves the patient's chances. Carotid angiography and electroencephalography may aid in the diagnosis in cases of longer duration.

Ventriculoplasty for Cardiac Aneurysm. C. P. Bailey, H. E. Bolton, H. Nichols and R. A. Gilman. J. Thoracic Surg. 35:37-67 (Jan.) 1958 [St. Louis].

The authors report on 9 patients with cardiac aneurysm who were operated on and of whom 8 survived in a much improved condition. The cardiac aneurysm usually involved the left ventricle and was of 3 types with respect to causation. One patient, a 7-day-old female infant, had a cardiac aneurysm due to congenital malformation, often described under the term "diverticulum." Two patients, 1 a 31-year-old woman and 1 a 38-year-old woman, had a cardiac aneurysm resulting from trauma produced by cardiac surgery for mitral and aortic stenosis, the aneurysmal sac being formed by extracardiac structures, especially the pericardium (false aneurysm). The remaining 6 patients, between the ages of 56 and 65 years, had a cardiac aneurysm resulting from weakening and bulging of a relatively localized area of myomalacia of the heart wall after myocardial infarction. Surgical treatment amounted to a subtotal resection of the aneurysm without the use of a cardiopulmonary bypass, enough of the mixed muscular and fibrosed basal tissue of the scar of healing being preserved to permit reconstruction of a ventricular chamber of approximately the normal size and shape for the particular patient. The appropriate term "ventriculoplasty" has been coined for this procedure. The technique has been described in a paper published in THE JOURNAL (158:915 [July 16] 1955).

Only 1 of the 9 patients died; he was the 2nd patient operated on for an aneurysm occurring after myocardial infarction, and death resulted from gross embolization at the moment of compression of the base of the aneurysmal sac which contained massive clotting. To prevent inadvertent dislodgement of such clotted material during the manipulations incident to the removal of the aneurysmal sac, a ventricular clamp armed with strips of Ivalon sponge was applied at the limits of the infarcted area into the normal muscle, a large incision was made into the infarcted area, and the wound was allowed momentarily to bleed. By this

V 1
195

method any contained clots would have been "flushed out." Since adopting the "flush-out" technique, and by continuing the use of the principle of ventriculoplasty (tailoring the ventricle) rather than attempting totally to excise all scarred tissue, there has been a gratifying surgical and clinical response from each patient so operated on. In view of the fact that no "revascularization procedure" was included in the operative technique, it is believed that all observed benefit was due to the removal of the physiological burden imposed by the paradoxically pulsating sac itself. With the increased incidence of surgical ventriculotomy, more ventricular aneurysms of traumatic (false) type may be expected to occur in the future. While every effort should be made to prevent their occurrence, they may be corrected with relative safety by the technique described.

In view of the gloomy outlook for patients with symptom-producing postinfarctional ventricular aneurysm, and the rather dramatic response to appropriate operative intervention, surgical consideration is strongly urged for these common, although less often recognized, sequelae of coronary arterial disease. Knowledge that an effective surgical method of treatment exists will stimulate an increased awareness on the part of the internist that such a lesion may exist. The diagnosis may be established with certainty by appropriate opacification techniques, and the patients may be referred for surgical treatment at a somewhat earlier stage, when the chances for survival and clinical cure will be greater, than was the case with the patients reported on, who were in the near-terminal or preterminal state.

Induced Cardiac Arrest (Cardioplegia) in Open Heart Surgical Problems. C. R. Lam, T. Gahagan, C. Mota and E. Green. Surgery 43:7-13 (Jan.) 1958 [St. Louis].

The authors began to study methods of producing cardioplegia in 1952. It was found that a solution of potassium chloride injected into the left ventricle produced arrest. Since they had no pump-oxygenator at that time, resuscitation had to be obtained by manual systole. This method of reviving the heart was undoubtedly largely responsible for the high incidence of ventricular fibrillation during the recovery phase. The authors then investigated the value of acetylcholine as a cardioplegic agent and found that ventricular fibrillation was less frequently encountered than during cardiac massage. It was also noted that the ideal way to resuscitate the heart was to perfuse the coronary arteries with oxygenated blood. When a pump-oxygenator of the bubble type became available to the authors early in 1956, they began to use it in open heart procedures, and the heart has been arrested with acetylcholine during the cardiotomy in all the 88 patients reported here. Fifty-eight of the operations have been for closure of ventricular septal defects, and 30 have been for correction of a great variety of congenital and acquired lesions. The method appeared to be safe and valuable for use in these open heart operations. The high death rate of 33% in patients operated on for closure of ventricular septal defects has been largely due to the fact that this group included 9 small infants who were operated on because they had ceased to grow and appeared to be near death. In contrast, in the group of children over the age of 3 years, the mortality rate was less than 5%.

Surgical Applications of Anterior Percutaneous Left Heart Puncture. D. G. Greene, J. T. Sharp, G. T. Griffith and others. Surgery 43:1-6 (Jan.) 1958 [St. Louis].

The suprasternal notch approach for left atrial puncture may be easily combined with direct anterior puncture of the left ventricle to permit measurement of pressure gradients across the mitral and aortic valves. For left atrial puncture the authors used the technique of Radner. A flexible needle, 18 cm. long and 0.8 mm. in outside diameter, is passed from the suprasternal notch posterior to the sternum and anterior to the trachea into the left atrium. It usually pierces the arch of the aorta and frequently the pulmonary artery as well on its way into the atrium. If so, pressures are measured in each of these structures on the way in and on withdrawal. If not, it is usually a simple matter to reinsert the needle into either of the great vessels if desired. The patient is supine with the neck extended and the head turned to the left. The needle is inserted in the midline. Once it is in place in the left atrium a second needle, usually a long, thin-walled 18 needle with a solid obturator, is inserted into the left ventricle through the anterior part of the chest wall. The chest is entered 1 to 2 cm. medial to the apex impulse in the 5th or the 6th left intercostal space, and the needle is directed medially, dorsally, and cephalad at an angle of 45 degrees with each of the major planes of the body. Once the cardiac impulse is felt with the tip, the needle is advanced quickly. The left ventricle is usually entered directly, or, less frequently, the right ventricle is pierced on the way into the left ventricle. It is usually easy to tell which ventricle one is in by the color of the blood. In case of doubt the systolic pressure may be compared with the systolic pressure in the systemic and pulmonary arteries, or a sample may be withdrawn for gas analysis.

The described techniques are well adapted for combination with catheterization of the right side of the heart and measurement of cardiac output by the direct Fick procedure. There have been few complications. In 18 patients whose pericardiums

were opened immediately after the procedure, no bleeding point was seen at the time of surgery. Usually 75 to 100 ml. of bloody pericardial fluid was found. In only 1 case was this amount exceeded, about 150 ml. being present. Two patients experienced hemoptysis after the procedure. In 1 patient this necessitated postponing the scheduled thoracotomy, while in the other the bronchi were cleared of blood by bronchoscopy. The 5 patients who did not undergo thoracotomy immediately after the procedure all had some chest pain for 1 to 4 days. Two had low-grade fever for the same period. The authors found that the combination of suprasternal puncture with direct anterior puncture of the left ventricle has the following advantages over catheterization of the left side of the heart: supine position, relative freedom from untoward sequelae, and lack of need for fluoroscopic control.

Ligation of the Inferior Vena Cava for Thromboembolism. W. A. Dale. Surgery **43**:24-44 (Jan.) 1958 [St. Louis].

Dale advocates nonoperative management of venous thrombosis and pulmonary embolism, reserving vein ligation for cases where anticoagulants are contraindicated or have failed. He reviews observations on 16 patients who eventually required vena caval ligation for thromboembolism. Thirteen of the 16 patients were operated on via the extraperitoneal approach from the right. Three were approached transperitoneally, once in order to remove the ovaries, once in order to explore the iliac veins, and once early in the series as a purely elective approach. The author comments on anomalies of the inferior vena cava, the collateral circulation, and venous pressure studies. In the postoperative management the prevention of edema is important, and the following measures are recommended: elevation of foot of bed; Ace bandages whenever out of bed; graded walking when pain permits; restriction of ambulation if edema occurs; restriction of sitting or standing; aeropulse boots; and contour chair. Prevention of further thrombosis is facilitated by the administration of anticoagulants and by thrombectomy if it occurs. Pain control is aided by medication and elevation of the legs. Maintenance of muscle power is effected by a program of weighted exercises for calves and thighs.

There was no operative mortality or further embolism in the 16 patients. While early postoperative leg edema was usual, the late leg complications proved to be minor if the legs were carefully managed. Three of 9 patients followed beyond 10 months have some edema or ulcer of the legs, although no patient has been incapacitated. Although anticoagulant drug therapy is advocated for venous thrombosis and/or pulmonary embolism in general, inferior vena caval ligation (rather than superficial femoral vein ligation) should be reserved for (*a*) failure of anticoagulant therapy, (*b*) contraindication to anticoagulants, and (*c*) thrombosis of pelvic veins (iliac, ovarian, prostatic, and so forth). Rare indications include septic pelvic phlebitis and phlegmasia cerulea dolens.

Pleurectomy for Recurrent Spontaneous Pneumothorax. P. A. Thomas and P. W. Gebauer. J. Thoracic Surg. **35**:111-117 (Jan.) 1958 [St. Louis].

The authors report on 11 men and 3 women, between 19 and 41 years of age, with recurrent spontaneous pneumothorax who were treated by thoracotomy, lung repair, and partial parietal pleurectomy. Excision of the parietal pleura was adopted to promote fixation of remaining lung tissue to the chest wall. The presence of multiple blebs and bullae, either in localized areas or generalized over the surface of the lung, was the predominant gross surgical pathological lesion which was found in most of these patients. Excision of the apical parietal pleura in the region of the disease process was performed in the first patient. Such a limited pleurectomy is now considered inadequate. The more complete operation, consisting of the removal of the parietal pleura over the chest wall and superior mediastinum, except for the diaphragmatic and pericardial reflections, is usually not difficult and was performed 14 times in 13 patients.

Pleurectomy is designed to produce 2 significant changes for the patient: (1) to obliterate the pleural space and prevent recurrence and (2) to provide revascularization of the peripheral portion of the lung in which pathological changes are usually most marked. There were no postoperative recurrences of spontaneous pneumothorax. Eight patients were asymptomatic. One of these required bilateral surgical intervention. In 3 patients the lung which was operated on was asymptomatic and stable as revealed by chest roentgenogram; however, one or more episodes of spontaneous pneumothorax of the unoperated lung occurred. These patients may require a second-stage surgical procedure on the remaining unstable lung. The postoperative course was entirely uneventful after 9 operations. A somewhat prolonged air leak was present in 2 patients, but recovery was uneventful. A minimal spontaneous pneumothorax of the unoperated side of the chest occurred in 1 patient, but recovery resulted without treatment. A small residual postoperative apical pneumothorax was observed in 2 patients. Of the 15 operations performed, only 1 resulted in a seriously complicated course with partial atelectasis of the lung which had been operated on. Bronchoscopy and thoracentesis were required as corrective measures. The characteristic preoperative findings of blebs, bullae, and parchment-like changes in the patients were

V 1
195

similar to some of the gross changes of pulmonary emphysema. They were suggestive of peripheral pulmonary ischemia. If they were to be considered as a precursor of later emphysema with primary or secondary vascular changes, pleurectomy should be performed more frequently than it has been in the past.

Spontaneous Bilateral Chylopneumothorax: A Case Report. R. A. Dillard and R. B. Perkins. J. Thoracic Surg. 35:91-96 (Jan.) 1958 [St. Louis].

The authors report a case of spontaneous bilateral chylopneumothorax in a 25-year-old man who was admitted to the Veterans Administration Hospital in Birmingham, Ala., with a chief complaint of shortness of breath for 1 week and dyspnea for 24 hours. Fluoroscopy revealed a fluid level up to the 4th intercostal space on the right. Thoracentesis on the right yielded 1,400 cc. of milky white fluid. The dyspnea decreased. The initial chest roentgenogram revealed the presence of air and fluid in both pleural spaces with partial collapse of both lungs. Intercostal catheter suction on the right was instituted but did not reexpand the lung. The chylous fluid continued to drain in large amounts. More air began to accumulate in the pleural space on the left, and dyspnea increased. Intercostal catheter drainage on the left removed 2 liters of chyle and much air. Ventilation improved. With clearing of the pleural space on the right of all fluid, enlargement of the superior mediastinal shadow on the right was observed on the chest roentgenogram.

Thoracotomy was performed and revealed that all pleural surfaces on the right were extensively replaced by tumor growing in sheets, with some areas thickened to form trabeculations. The lung was about 75% collapsed, affecting all 3 lobes equally. The visceral pleura was replaced by a thin layer of this tissue, which puckered the lung in areas. There were many minute air leaks, the source of the pneumothorax. The chyle appeared to rise from many areas over the mediastinal parietal surfaces, and there was no intercommunication between the pleural spaces or localized disruption of the thoracic duct. Diagnosis of a malignant mesothelial cell growth was made on frozen sections. Although the attempt at decortication was not successful, the thoracic duct was ligated just above the diaphragm and dissected proximally for 4 in. and excised. Three large thoracostomy tubes were left in the pleural space. Microscopic examination of permanent sections revealed malignant mesothelioma of the pleura, composed of uniform cells growing in sheets and strands, separated by a dense corrective tissue stroma. The cells showed vesicular nuclei, prominent nucleoli, and pale cytoplasm. The postoperative course was characterized by continued drainage of chylous fluid and gradual deterioration. The patient died 20 days after thoracostomy. Autopsy revealed complete involvement of visceral and parietal pleura bilaterally with growth over the pericardium. The tumor extended into and below the diaphragm to involve the liver, the right adrenal, and the kidney.

A review of the literature did not reveal a similar case of spontaneous bilateral chylopneumothorax or any other case of chylous fluid associated with a pleural mesothelioma. It must be postulated that the cause of the nontraumatic chylothorax was compression, invasion, or occlusion of the thoracic duct by the tumor growth at multiple sites. The patient did not benefit from the attempted decortication of the right lung and ligation of the thoracic duct.

Primary Leiomyosarcoma and Leiomyoma of the Lung: Review of the Literature and Report of Two Cases of Leiomyosarcoma. J. W. Agnos and G. W. B. Starkey. New England J. Med. 258:12-17 (Jan. 2) 1958 [Boston].

The 2 new cases of primary pulmonary leiomyosarcoma presented concerned men, aged 52 and 57 years respectively. A review of the literature on smooth muscle tumors of the lung revealed 14 cases of leiomyoma and 18 of leiomyosarcoma. Some of the pulmonary leiomyomas were detected by routine chest films, whereas all the leiomyosarcomas had produced symptoms. The commonest presenting symptoms of the leiomyosarcomas were cough, dyspnea, chest pain, and sputum. Roentgenologic investigation was positive in all cases, showing a mass with or without atelectasis. The leiomyosarcomas were frequently visualized bronchoscopically. Biopsy was positive for tumor in half of the cases in which biopsy specimens were obtained. In most cases, the treatment consisted of surgical excision. Excellent results were obtained with the leiomyomas. The outcome with the leiomyosarcomas was better than that seen with primary carcinoma of the lung.

Carcinoma of the Parathyroid. G. L. Jordan Jr., G. W. Curd, F. Gyorkey and M. E. DeBakey. A. M. A. Arch. Surg. 76:87-92 (Jan.) 1958 [Chicago].

The authors present a report on a 42-year-old man who had most of the classic features of hyperparathyroidism. The history of chronic dyspepsia, weakness, muscle aches, chemical abnormalities, and metastatic calcification, the evidence of renal impairment, and the absence of the lamina dura were characteristic. It was possible to suspect the diagnosis of carcinoma, owing to the fact that the lesion was large enough to be palpable, that it was hard, and that there was an associated paralysis of the recurrent laryngeal nerve on the same side as that on which the lesion was palpated. An interesting feature was the development of pancreatitis in the postoperative period. Why pancre-

atitis should occur after surgery on the parathyroid gland is not clear, but its frequency appears to be greater than one would suspect. The patient also presented the interesting phenomenon of elevation of blood pressure in the postoperative period. Tests for pheochromocytoma did not confirm the presence of this tumor, but the possibility that the patient might have multiple neoplasms of the endocrine glands cannot be completely excluded. The condition may also have been related to his renal disease.

The prognosis for patients with carcinoma of the parathyroid is not well documented in view of the paucity of clinical experience with this disease. The commonest tumor involving the parathyroid is benign adenoma; carcinoma is quite rare. Several reports on cases of carcinoma of the parathyroid suggest that these patients may live many years, even with the presence of metastatic disease. The possible beneficial effects of a radical neck dissection in the absence of palpably enlarged nodes cannot be settled. Distant metastases seem to be as common as metastases to cervical nodes. If the primary tumor is a functioning one, it appears likely that metastatic lesions will also show function. Consequently, careful follow-up examinations are indicated, and if hyperparathyroidism recurs, an effort should be made to localize and surgically remove areas of recurrence.

Reconstruction of the Esophagus with Segments of the Colon. W. E. Neville and G. H. A. Clowes Jr. J. Thoracic Surg. **35**:2-22 (Jan.) 1958 [St. Louis].

To evaluate the reconstruction of the esophagus by implanted colon, the esophagus was resected from the inferior pulmonary vein to the cardioesophageal junction in 6 normal dogs. An appropriate segment of transverse colon was interpolated in isoperistaltic fashion between the esophagus above and a separate opening in the fundus of the stomach. A colocolostomy reconstituted the colon. Pyloromyotomy or pyloroplasty provided adequate drainage of the vagotomized stomach. The dogs were killed at varying periods up to 9 months after the operation, and the postmortem findings were compared with those in 5 dogs which had been killed at varying periods up to 3 months after resection of the distal end of the esophagus and an esophagogastrostomy, bilateral vagotomy, and pyloromyotomy or pyloroplasty. In none of the 6 animals in the first group was there evidence of esophagitis, colitis, or gastritis. The animals in the second group showed diffuse inflammation in the stomach and ulceration of the esophageal mucosa. These results lend support to the concept that the stomach is not a good substitute for the esophagus. In contrast to that, the colon appears to meet the requirements for a satisfactory substitute, since it has sufficient length, since it is assured of continuing viability, and since its lining is resistant to acid peptic digestion. The colon also has an excellent blood supply.

Consequently, the technique of reconstruction of the esophagus with segments of the colon was used in 28 patients, 23 of whom had carcinoma and 5 had benign disease of the esophagus. The average operating time on all the patients was 3½ hours. There were 7 deaths in the immediate postoperative period, which occurred in patients with carcinoma above the aortic arch. Five additional patients died of a progression of their disease or of coronary occlusion after an average survival time of 8 1/3 months. Sixteen patients are living and have been followed from 3 to 36 months. All have a normal appetite with normal ingestion of food. Fifteen patients have an improved nutritional status and have gained weight. Hemoglobin levels, hematocrit, and serum protein determinations have been normal in all patients at one time in the postoperative period. The commonest nonfatal complication was diarrhea. This occurred in 8 of the 16 surviving patients and in all the experimental animals. It was associated with ingestion of food, but it usually persisted for only a few weeks. Empyema without a demonstrable anastomotic leak occurred in 2 patients who responded satisfactorily to frequent early aspiration and subsequent open drainage. Three patients complained of nocturnal regurgitation. Atelectasis was a disturbing complication in resecting high intrathoracic carcinomas. Collapse of the right lung occurred soon after the operation in 4 older patients who responded satisfactorily to bronchoscopy and tracheostomy. Narrowing of the esophagocolon anastomosis in the neck occurred in 2 patients; revision was successfully carried out in both patients. The large intestine is seemingly resistant to peptic ulceration clinically, even though reflux of barium into the colon segment can be demonstrated fluoroscopically; no evidence of colitis could be seen on routine esophagoscopy and postmortem examination up to 20 months after implantation.

Tracheobronchial Rests in the Esophagus: Their Relation to Some Benign Strictures and Certain Types of Cancer of the Esophagus. M. Bergmann and R. M. Charnas. J. Thoracic Surg. **35**:97-104 (Jan.) 1958 [St. Louis].

The authors report the occurrence of a benign stricture of the esophagus in a 57-year-old woman with the chief complaint of dysphagia since childhood. A 3-cm. segment of the esophagus bearing the stricture was excised, and esophageal continuity was restored by end-to-end anastomosis. Microscopic examination of the operative specimen showed gland-like structures deep in the esophageal wall, which were lined by typical respiratory epithelium, such as is usually found in the trachea or the major bronchi. The epithelium-

lined structures were surrounded by lymphoid follicles and a marked chronic inflammatory reaction. Congenital remnants were directly responsible for the occurrence of the localized esophageal stricture in this patient. A similar case of an intramural diverticulum of the esophagus lined by tracheobronchial epithelium, which had been termed an abortive tracheoesophageal fistula, was reported in the literature.

The concept that the persistence of tracheobronchial rests in the esophageal wall might give rise to tumors of the esophagus was supported by the authors' report of the case of a 65-year-old man with dysphagia and an obstructive lesion of the esophagus revealed by roentgenography and esophagoscopy. Subtotal esophagectomy was performed, and microscopic examination of the operative specimen revealed a structure whose histological features closely resembled those typical of the malignant cylindromatous tumors of the tracheobronchial tree. Such a lesion had not previously been reported. However, reports on 2 cases of typical oat-cell carcinoma (indistinguishable from oat-cell cancer of the lung) occurring in the esophagus were collected from the literature. The occurrence of these tumors is best explained by assuming an origin in tracheobronchial rests in the esophagus, such as was found in the patient with the benign obstructive lesion of the esophagus.

Jaundice Due to Tumors and Other Disorders of the Ampulla of Vater and Head of the Pancreas. M. W. Van Weel. Nederl. tijdschr. geneesk. **101:** 2203-2208 (Nov. 23) 1957 (In Dutch) [Amsterdam].

Observations were made on 71 patients with obstructive jaundice due to tumors. The majority had carcinoma, which in 14 involved the ampulla of Vater, in 6 the choledochus, in 44 the head of the pancreas, and in 2 the duodenum. Four patients had chronic pancreatitis, and 1 had a stenosal papillitis. A total of 74 operations were performed. Seventeen pancreaticoduodenectomies were performed, and 3 of the patients who were operated on died. Three patients had transduodenal excisions, and none died. Various biliary system digestive operations were performed in 44 patients, and 5 of these died. The biliary system operations were cholecystogastrostomy, cholecystoduodenostomy, cholecystojejunostomy, and choledochoduodenostomy.

Pancreaticoduodenectomy signifies a considerable step forward in the treatment of tumors of the duodenopancratic region. Even when this operation was not radical, the life of the patient was considerably prolonged, and there was a much greater effect than was achieved with the biliary tract digestive anastomoses. The primary mortality from pancreaticoduodenectomy is by no means negligible, and careful consideration should be given to whether the patient should be exposed to this risk. The prognosis of malignant tumors of the duodenopancreatic organs is unfavorable. It may be improved by early recognition of mechanical jaundice. In patients in whom obstructive jaundice is suspected, exploratory laparotomy should be performed as early as possible.

Massive Hemorrhage from Peptic Ulcer: A Cause of Myocardial Infarction in the Aged. W. L. Craver and F. Glenn. J. Am. Geriatrics Soc. **5:**969-981 (Dec.) 1957 [Baltimore].

Massive hemorrhage is defined as that degree of blood loss which threatens life, and the following criteria are listed: (1) hematocrit reading of 30% or less (normal, 44%); (2) hemoglobin level of 10 Gm. per 100 cc. or less (normal, 14.5 Gm. per 100 cc.); (3) red blood cell count of 3.5 million per cubic millimeter or less (normal, 5 million per cubic millimeter); and (4) clinical evidence of acute blood loss from the gastrointestinal tract. In the 10-year period from Jan. 1, 1946, to Dec. 31, 1955, there were 53 patients, over 65 years of age, admitted to the New York Hospital-Cornell Medical Center with hemorrhage from a peptic ulcer. Thirty of these patients met all the foregoing criteria. Most of the patients were free from symptoms prior to the hemorrhage, thus they had no warning of impending activity and bleeding of the ulcer. In over a fourth of the patients who bled prior to admission, bleeding continued or recurred in the hospital. In the 17 patients treated medically, 3 definite myocardial infarctions and 1 possible one occurred. There were no myocardial infarctions in the 13 patients treated surgically. There should be prompt and adequate replacement of blood, to prevent shock and avoid coronary insufficiency. If bleeding continues or recurs, early operation is imperative.

Carcinoma Arising in Sebaceous Cysts. J. W. Welch. A. M. A. Arch. Surg. **76:**128-132 (Jan.) 1958 [Chicago].

Welch emphasizes that the sebaceous cyst should not be considered as a precancerous lesion, for the incidence of malignant degeneration of sebaceous cysts thus far reported in the literature and in this study is no greater than one would expect, considering the age incidence and other causative factors. Of the 239 cutaneous cysts removed and microscopically examined at the Hertzler Clinic in Halstead, Kan., during the last 3 years, 128 proved to be benign sebaceous cysts, whereas 6 were carcinomas with definite origin in sebaceous cysts. The remaining 105 were varieties of epidermoid cysts, of which 3 were malignant. The incidence of malignancy arising in sebaceous cysts in this series was 4.7%, according to the stricter criterion, or 3.7%, according to the broader interpretation of

sebaceous cysts. At least 1 singular finding, that of simultaneous multiple sebaceous cyst malignancies, evolved from the study, and the case history is presented. A review of the literature revealed no histological standard differentiation between a sebaceous cyst and an epidermoid cyst. In all cases of malignancy here presented, the preoperative diagnosis was benign sebaceous cyst. In the entire investigation only a few lesions were correctly diagnosed preoperatively as epidermoid cyst, the usual diagnosis being benign sebaceous cyst.

The structure of these carcinomatous cysts does not vary greatly. The cyst cavity commonly contains a hornified material, while the cyst wall is composed of well-differentiated cells with strands of squamous cells invading the stroma. There is, as a rule, considerable tendency toward hornification, pearl formation, and intracellular spines. The basal-cell carcinoma and the basosquamous-cell carcinoma exhibit marked proliferation of basal cells, which invade the stroma or the cyst wall. For the most part, the malignancy is of low grade. The treatment for this lesion is early complete excision, to include a generous margin on all sides of the tumor. This is particularly urgent if there has been any recent trauma or change in size or character. Surgery becomes imperative if there has been any history of previous malignancy in addition to trauma or change in size or character. The occurrence of 1 or more additional primary neoplasms in a patient already afflicted with one such lesion is 6 or 7 times as likely as the 1st occurrence of a malignancy in an unafflicted patient.

A Comparison of Thoracolumbar Sympathectomy and Adrenalectomy with Adson Sympathectomy in the Treatment of Severe Arterial Hypertension: A Three-to-Seven-Year Follow-up Report. W. S. Blakemore, H. A. Zintel, W. A. Jeffers and others. Surgery **43**:102-112 (Jan.) 1958 [St. Louis].

Subtotal or total adrenalectomy combined with a limited sympathectomy has been used at the Hospital of the University of Pennsylvania for more than 7 years for severe essential hypertension. This paper compares the results of treatment of 2 similar groups of patients; 1 group composed of 116 patients was treated by this operative procedure, and the other comprising 114 patients by bilateral thoracolumbar sympathectomy. All patients were followed from 3 to 7 years after operation. The criteria for selection of the patients for surgery included the following: (1) severe disease as measured by diastolic pressures of 120 mm. Hg or greater; (2) evidence of progressive vascular damage to the brain, heart, eyes, or kidney; (3) failure to respond to vigorous medical therapy; (4) age of not more than 55 years; and (5) no vascular accident to the brain or heart within the past 6 months. Initially those with advanced renal failure were accepted for operation, but it was soon learned that these patients did not respond favorably. Subsequently the authors considered as contraindications to either operative procedure phenolsulfonphthalein excretion of less than 15% in 15 minutes and a blood urea nitrogen level consistently above 20 mg. per 100 cc.

The surgical mortality was less than 1% for patients in the thoracolumbar sympathectomy series and 5% for those who had an adrenalectomy in addition to some form of sympathectomy. Seventy-three per cent of the patients who had a thoracolumbar sympathectomy survived during the follow-up period, compared with 68% of those having an adrenalectomy. The effects upon blood pressure levels, electrocardiogram, heart size, and ocular fundal changes were superior after adrenalectomy. Angina and congestive failure seemed greatly relieved especially after adrenalectomy. Headache was relieved by both operative procedures. The degree to which these patients can be rehabilitated is encouraging.

Epiphysiodesis. C. P. Van Nes. Arch. chir. neerl. **9**:371-383 (No. 4) 1957 (In English) [Arnhem, Netherlands].

Epiphysiodesis is the intentional early arrest of growth of an epiphysial disk in order to reduce the longitudinal growth of a skeletal part. Consequently it is used only during the period of growth. The author discusses lasting and temporary arrest of growth. Lasting arrest of epiphysial growth can be effected by Phemister's method or by one of its modifications. Phemister removed an oblong portion of the cortical layer on the inside and the outside of the epiphysial disk; the adjacent epiphysial disk was then partially scooped out, after which the piece of bone was rotated 180 degrees, thus displacing the epiphysial cartilage contained in it to a higher level in the shaft. The bolting effect of the operation is questionable; undoubtedly its most important feature is the scooping out of the epiphysial disk. In order to facilitate the total removal of the disk, the Phemister technique was modified as follows: a piece of bone, pyramidal in shape and extending as deeply as possible into the spongy layer, is chiseled out at the level of the epiphysial disk. After its removal, the epiphysial disk is scooped out. The piece of bone is then rotated 90 degrees and driven firmly into its former bed. This treatment is applied to the leg on the median and lateral sides. In the case of epiphysiodesis below the knee the proximal epiphysial disk of the fibula is also scooped out.

Temporary arrest of epiphysial growth has been described by Blount, who fixed 3 strong staples vertically across the epiphysial disk, driving 1 of the legs of the staple into the metaphysis and the other into the epiphysis. The author did not use the

V 1
195

method of Blount in the equalization of limb length, because he obtained satisfactory results by means of lasting epiphysiodesis. A total of 265 epiphysiodeses were performed in 211 patients, on the lower extremities in 205 and on the upper extremities in 6. The operation was used for correcting differences in lower limb length, resulting from paralysis, congenital anomalies, coxitis or gonitis, war injuries, and osteomyelitis, and for correction of the sequelae of trauma of the upper limbs. In 69% of the cases the difference in limb length was less than 2 cm. after completion of growth. In many cases a certain difference in limb length was intentionally retained. Untoward effects attributable to epiphysiodesis were observed in none of the patients.

NEUROLOGY & PSYCHIATRY

Chromophobe Adenoma of Hypophysis: Nosography. E. Andersson. Ugesk. læger **119**:1521-1524 (Nov. 21) 1957 (In Danish) [Copenhagen].

Among 172 cases of histologically confirmed adenomas of the hypophysis from the neurosurgical department of the Rigshospital, 119 were chromophobe adenomas. Eye symptoms dominated in 110 cases; hypophysis deprivation symptoms, in 9 cases. Most cases occurred between the ages of 30 and 60 years; the youngest patient was 12 years old. The disease apparently occurs about equally frequent in the two sexes. The symptoms are either predominantly neurological, due to pressure of the tumor on the surrounding nervous tissue after it has broken out of the sella turcica, or predominantly endocrine, due to insufficiency of the hypophysis, depending on pressure atrophy because of the growth of the tumor in the sella turcica. Disturbances in vision were among the first symptoms recognized in 110 of the patients. The neurological symptoms in most cases become marked only in patients untreated for a long time or having rapidly growing tumor. Gonadotropic deficiency symptoms are the most common hormonal disturbances and seem to appear relatively early. A chromophobe adenoma should be considered in hypopituitarism. Hypogonadism with myxedema and insufficiency of the adrenal cortex testifies for disease of the hypophysis. Routine roentgenologic examination of the sella turcica and determination of the field of vision should always be carried out. Both hypophysis myxedema and primary myxedema should be borne in mind in the case of a patient with lowered metabolism. If myxedema is suspected as being due to a chromophobe adenoma, thyroidin must never be given without checking on the functioning ability of the adrenal cortex. The chief symptom in insufficiency of the adrenal cortex in hypopituitarism is fatigue. Addison's crisis occurs only if the patient is exposed to stress, grave infection, extreme muscular effort, and overdosage of medicaments, such as thyroidin or insulin. In hypopituitarism most patients can avoid great metabolic changes as long as they follow a normal diet.

Prognosis in Patients with Gliomas of Cerebral Hemispheres. I. Papo and R. Tritapepe. Minerva med. **48**:4054-4060 (Dec. 1) 1957 (In Italian) [Turin, Italy].

The authors review the prognosis in 426 patients with intracranial tumors, who were operated on during the period between 1934 and 1954. Glioblastoma of the cerebral hemispheres was found in 200 patients. There were 34 operative deaths, while 13 patients (10%) survived for more than 2 years. Astrocytoma of the cerebral hemisphere was encountered in 138 patients, of whom 20 died because of the operation; 41 patients (40%) survived for more than 2 years, and 29 (29%) survived for more than 3 years. The histological distinction between glioblastoma and astrocytoma was not always clear-cut because of the cytological and structural variations observed in different sections of the same tumor, particularly when only a small fragment of tissue was first available for biopsy at operation, and later the whole tumor was reexamined at autopsy. Patients with astrocytoma survived slightly longer than those with glioblastoma; however, since the nature of both is malignant, the prognosis is fatal. Oligodendroglioma of the cerebral hemisphere was present in 44 patients. The operative mortality was 5%. Twenty-two patients (50%) survived for more than 3 years. The prognosis in patients with oligodendroglioma is also fatal, although the survival time is slightly longer than in those with glioma. The 4th group consisted of 44 patients with immature or atypical intracranial tumors. Eight patients died because of the operation, and 5 survived for more than 2 years.

Astrocytomas and oligodendrogliomas were more frequent in patients below the age of 40 years, and glioblastomas in those above the age of 50. Patients with gliomas confined to the frontal lobe had a better prognosis than those in whom gliomas were located in the parietal or the occipital lobe. The histological nature, the growth process, and the accompanying pathological features of the tumor (necrosis, hemorrhage, cerebral edema) are more important in the prognosis of the survival time of the patient than the localization or the size of the tumor. The authors do not believe that surgical intervention can eradicate the growth of glioblastoma, although treatment by decompression will give the patient temporary relief. Surgical removal of astrocytomas or oligodendrogliomas affords a chance of survival for longer periods of time than the mere surgical biopsy.

Two Classic Cases of Hepatolenticular Degeneration. O. Lingjærde. Tidsskr. norske lægefor. 77: 1039-1042 (Dec. 1) 1957 (In Norwegian) [Oslo].

The author queries whether 4 main types of hepatolenticular degeneration must be reckoned with: (1) a classic type with both hepatic and neurological and psychic symptoms; (2) a type with dominating neurological symptoms; (3) a type with dominating hepatic symptoms, the so-called abdominal Wilson type; and (4) a type dominated by psychotic symptoms. Only biochemical investigations can give the answer. In 2 of the 3 cases described, the classic symptoms were present, and the pathological findings were typical; one case was of the Westphal-Strümpell type, the other was of the Wilson type. The third case of probable hepatolenticular degeneration was that of a younger brother of the patient with the Wilson type. A sister of the first patient was characterized as mentally diseased.

The Immune Status of Poliomyelitis Patients. J. C. Wilt, W. Stackiw, J. A. Hildes and others. Canad. M. A. J. 78:32-34 (Jan. 1) 1958 [Toronto].

The study was undertaken to determine whether poor circulating antibody response is related to susceptibility to paralytic poliomyelitis. In a group of patients who had had paralytic poliomyelitis, the level of circulating antibodies was measured before, during, and after poliomyelitis vaccination, and the results were compared with those in a group of healthy controls studied concurrently. Forty-nine patients were included in the study, 28 males and 21 females, ranging in age from 6 to 67 years. Forty of the patients were still in hospital with respiratory paralysis. The diagnosis of poliomyelitis was unequivocal, and all had considerable residual paralysis. At the time of this study the patients were in good general health. Forty-three control subjects were also studied. All were adults, and most were employees of the hospital. All were in good health. None had had a clinically recognized attack of poliomyelitis, although most of them had been residents in epidemic areas.

The response varied in individuals, but the patients as a group responded as well as the controls did. The most evident difference between the 2 groups was in the incidence of antibodies in the prevaccination blood samples, which demonstrated that a higher proportion of patients than controls had circulating antibodies to a single virus type and that a higher proportion of controls than patients had antibodies to all 3 types of virus. A significantly higher proportion of controls had antibodies to type 2 virus, which suggests that type 2 virus offers some protection against infection with types 1 and 3.

Neuropsychiatric Symptoms in Liver Insufficiency. B. Harvald and M. Bjørneboe. Ugesk. læger 119: 1451-1457 (Nov. 7) 1957 (In Danish) [Copenhagen].

Of 19 patients with liver insufficiency observed during a 14 months' period in the medical department of Blegdam Hospital, 4 had alcoholic cirrhosis, 9 probably had chronic hepatitis, 4 had subacute hepatitis, and 2 had chronic hepatitis and portacaval anastomosis. Six patients died during the observation time. In most cases symptoms from the central nervous system developed after the other symptoms of progressive liver insufficiency, but in 3 cases symptoms from the central nervous system were the first signs of liver insufficiency. Three patients at times developed a Parkinsonian-like rigidity. With the development of neurological deficiency symptoms, the patient's psyche was affected. At first there was a mild confusion, then deep coma. Many of the patients became psychically clear after one or more attacks of coma, even without specific therapy. Confusion, flutter, and an abnormal electrocardiogram are a characteristic triad which marks beginning hepatic coma. In several cases the symptom of flutter led to the diagnosis of a hepatic coma. The type of dementia in hepatic coma does not differ from other forms of organic dementia, but it is peculiar in its frequently variable course. Considerable value is ascribed to treatment with diet low in protein and sterilization of the intestinal contents (Sherlock). The authors stress that hepatic coma does not inevitably lead to death but that it appears, especially in chronic liver diseases, in a recurring form which is to a certain degree responsive to therapy and prophylaxis. In patients with portacaval anastomosis one must be prepared to meet this symptom complex, and recognition and correct treatment are of great significance for the fate of the patient.

Epidemiologic and Prophylactic Considerations Concerning a Recent Epidemic of Poliomyelitis in Verona. A. Del Campo and S. De Marco. Minerva med. 48:4074-4079 (Dec. 1) 1957 (In Italian) [Turin, Italy].

Two major epidemics of poliomyelitis occurred in the city of Verona in the last 20 years. In the epidemic of 1941 there were 147 cases and in that of 1953, 229 cases. Each epidemic was preceded by a period of 2 years, in which a sharp increase in the incidence of the disease was followed by a remission of the endemic. Another epidemic, comprising 96 cases (45 in the urban area and 51 in the rural area), occurred in the province of Verona in 1957. The monthly distribution of the incidence of the disease was as follows: 8 cases in April and the first half of May, 13 in the second half of May, 33 in June, 23 in July, and 16 in August. The patients included 40 males and 47 females between the

V 1
195

ages of 6 months and 14 years. The disease had the highest incidence among the 56 patients in the youngest group, from below 1 year to 3 years of age, with a decreasing incidence among the older groups; the latter included 22 patients in the group 3 to 6 years of age, 9 in the group 6 to 9 years, 6 in the group 9 to 12 years, and 3 older than 13 years. There was a short incubation period manifested by paralysis of the limbs in 78 patients, by paralysis of the cranial nerves in 12, by bulbar form in 3, and by meningeal form in 3. Poliomyelitis was fatal in 3 patients, all of whom had the bulbar form of the disease. The isolated virus was established to be of type 1. Spread of the infection occurred mostly by contact of a healthy person with a healthy carrier of an inapparent infection.

The first antipoliomyelitis vaccination (Salk vaccine) was introduced in Italy during this epidemic; administration was on a voluntary basis. The vaccine was given to 324 children, none of whom contracted the clinical disease. The authors believe that antipoliomyelitis vaccination is not contraindicated during an epidemic of poliomyelitis.

GYNECOLOGY & OBSTETRICS

The Value of the Vaginal Smear in the Treatment of Disorders of Menstruation. M. E. Egerton. J. Obst. & Gynaec. Brit. Emp. 64:827-835 (Dec.) 1957 [London].

Doubt has been expressed as to whether the results of screening for uterine cancer alone justify the expenditure of time and money involved in the routine examination of vaginal smears. It is sometimes forgotten that the test has an additional application as an index of ovarian function. Vaginal and cervical smears were taken from 1,970 patients attending the gynecologic clinics of the Royal Free Hospital, London, between the years from 1953 through 1956. In an effort to assess the value of the test as a routine measure in gyneco'ogic practice, both smears were screened for cancer, and the vaginal smear was examined for evidence relating to ovarian function. It was found that many patients with menstrual disorders gave smears which differed markedly from the accepted norm, and that treatment with estrogen or progesterone, as indicated by the smear, did in many cases not only bring about an approximation to the accepted cytological pattern but also resulted in an amelioration of symptoms. Caution should be exercised when interpreting isolated smears, because a high cornification percentage is not necessarily an indication of high estrogen levels. This fact should not discourage a wide use of the test, which merits extended application, increasing study, and serious efforts to correlate it with biochemical and other investigations. The work described has led to the continued use of vaginal cytology in the gynecologic department of the Royal Free Hospital, London.

Some Observations on Cancer of the Breast in Mothers and Daughters. P. Bucalossi and U. Veronesi. Brit. J. Cancer. 11:337-347 (Sept.) 1957 [London].

Eighty-one patients with breast cancer, whose mothers had also been afflicted by the same disease, were regarded as belonging to "high mammary cancer strains," this being confirmed by the high incidence of breast cancer in their sisters (namely, 15 times as great as in the general population). The comparison carried out between these 81 cases and a series of 3,886 breast cancer cases observed in the Cancer Institute of Milan showed no differences as regards (1) baby feeding, (2) site in breast and histological type of tumor, or (3) marital state and parity. The length of menstrual life, supposed to be an expression of ovarian activity, proved to be slightly greater, as menopause occurred later in the 81 women of this series, both in comparison with patients in another breast cancer series and in comparison with the control series. The age of onset of the disease in 56 patients proved to be about 4 years lower than it was in the case of their mothers. In 2 patients cancer showed itself after prolonged, even if not intensive, estrogen therapy. From this study it would appear probable that the "familial" factor favorable to the rise of breast cancer resolves itself into a "genetic" factor; its possible mechanism of action (either by the production of an abnormal hormonal stimulation or by an increased sensitivity of mammary tissue to hormones) is briefly discussed.

A Case of Chorionepithelioma of the Uterus with Pulmonary Metastases Cured by Operation and X-Rays. F. J. Browne. J. Obst. & Gynaec. Brit. Emp. 64:852-856 (Dec.) 1957 [London].

A 25-year-old woman was hospitalized and came under the author's care in March, 1947. She had passed a hydatidiform mole in April, 1946, and uterine curettage had been done at that time. After that she had menstruated regularly from August to December, 1946, her last menstrual period being from Dec. 10 to 16. She had bled every day from Dec. 20 till admission. During this interval she had had repeated curettings and Aschheim-Zondek tests. The tests were consistently negative, and curettings failed to show evidence of malignancy. The curettings obtained in March, 1947, gave no evidence of recent pregnancy but rather suggested a malignant condition; the author suspected chorionepithelioma, but a pathologist decided that, in view of negative Aschheim-Zondek reactions, a diagnosis of choriocarcinoma was not justified. Later there was recurrence of bleeding, and the woman

was kept under observation. A panhysterectomy was carried out in June, 1947. There was a small nodule about the size of a pea in the right broad ligament. There did not seem to be any other extrauterine extensions. The removed uterus showed a large growth on the posterior wall of the lower uterine segment.

Examination of the surgical specimen established the diagnosis of chorionepithelioma. A chest x-ray showed multiple secondary deposits in both lung fields. The bilateral pulmonary metastases disappeared after x-ray treatments. The salient features of this case are (1) the difficulty in diagnosis from curettings, (2) the rather misleading results of Aschheim-Zondek tests, (3) the disappearance of multiple metastases in both lungs after x-ray therapy, and (4) the patient remaining well for 10 years after the treatment. Approximately 20 cases have now been reported in which pulmonary metastases disappeared either spontaneously or after x-ray treatment of the lungs. The presence of pulmonary metastases should not be regarded as a contraindication to removal of the primary tumor.

A Simple Cytological Test for Cancer Cure. E. Wachtel. Brit. M. J. 1:20-22 (Jan. 4) 1958 [London].

The author reports on 165 women, between 24 and 80 years of age, who had received treatment for such malignant conditions of the genital tract as carcinoma of the vulva, Paget's disease of the vulva, squamous carcinoma of the cervix, adenocarcinoma of the endocervix, endometrial carcinoma, and carcinoma of the ovaries. The patients were followed up for periods of from 1 to 10 years at the Gynecologic Cancer Follow-up Clinic of the Hammersmith Hospital in London. Vaginal smears were obtained from these patients at each attendance at this clinic, and the cornification index, implying a count of 200 consecutive superficial and intermediate squamous cells and determination of the percentage of those with pyknotic nuclei (cornified cells), as well as the presence or absence of malignant cells, was recorded.

One hundred eleven of the 165 patients showed no evidence of any clinical, histological, or cytological recurrence and had cornification index readings of below 10. Thirty-seven patients had cornification index readings of over 10, and other evidence of remaining disease was found later. Nearly all these recurrences were cytologically predicted, that is, the high cornification index was the first evidence of remaining disease; in only 7 patients was clinical evidence of persisting malignant growth present at the time the cytological prognosis was made. Nine patients had cornification index readings of over 10 and no clinical evidence of recurrence, and they remain under observation; in 4 of these the time elapsed since completion of radical treatment has not yet exceeded 6 months. There was clinical and histological evidence of recurrence without rise in cornification index in 8 patients. A low cornification index reading during the observation period after completion of treatment should be regarded as a favorable prognostic sign only in patients in whom the pretreatment cornification index was high.

Accurate forecasts, relying solely on cornification index readings, thus were made in 94.8% of the 165 patients. Cornification index estimations in patients who received radical treatment for malignant disease in the genital tract seem to be of great diagnostic help in the recognition of failure of response or in the detection of early recurrence. The frequency with which a high cornification index reading is associated with malignant disease in the female genital tract is significant enough to suggest the use of it as a test for cure. The technique of cornification index estimation is easy and can be learned in a short time. Cornification index estimation should be included in the routine cytological follow-up investigations of cancer in view of the important implication of this test.

Possibilities and Limitations of Oral Cholecystography for the Diagnosis of Biliary Tract Diseases in Last Trimester of Pregnancy. A. Tetti and G. L. Sannazzari. Minerva ginec. 9:734-741 (Sept. 15) 1957 (In Italian) [Turin, Italy].

Diagnostic reliability of oral cholecystography for biliary tract disease was studied in a group of 30 normal prima-gravida women in the last 3 months of pregnancy. They received an oral dose of Telepaque the evening preceding the roentgenologic examination. A cholecystokinetic meal, followed by taking a film every half-hour for 2 hours, enabled the authors to observe the emptying function of the gallbladder. The films showed a gradual displacement of a deformed gallbladder shadow upward to the right. The shadow looked compressed against the lower side of the liver in some of the women; this was caused by the enlarged uterus. Several cholecystograms showed an enlarged gallbladder shadow. Satisfactory visualization of the gallbladder was obtained in all the women except 4; 3 of these were near term, and 1 was in the 8th month of pregnancy. Storage of bile in the gallbladder appeared to be normal in one-half of the women whose films showed a shadow with satisfactory intensity and definition. The films of the remaining women showed a faint shadow, which was more frequent among those near term. Motor function of the gallbladder was not consistent in all the women after the cholecystokinetic meal; it appeared to be more intense, equal, or less intense than the normal physiological function.

The authors conclude that oral cholecystography based on modern contrast mediums is of no help for a roentgenologic diagnosis of calculosis asso-

ciated with inability of bile expulsion, of cholecystitis without calculi, and of biliary dyskinesia. Oral cholecystography is helpful in discarding the roentgenologic diagnosis of a clinically suspected incidence of cholecystitis.

OPHTHALMOLOGY

Bilateral Loss of Vision from Cerebral Infarction. C. Symonds and I. Mackenzie. Brain **80**:415-453 (Dec.) 1957 [London].

Loss of vision in both half-fields as the result of cerebral infarction is rare. Hemianopsia is not uncommon in hemiplegia from infarction, and a subsequent vascular lesion in the other hemisphere may cause loss of the remaining visual fields. Such cases are not considered in this paper, which is concerned with the study of bilateral visual loss from infarction of the occipital lobes. The authors review 29 cases from the literature in which loss of vision in both halves of the visual fields was associated with the postmortem observation of bilateral occipital lobe infarction. The clinical data on 20 cases from the literature in which comparable symptoms were observed without postmortem examination are summarized. Nine observations of the syndrome are presented, 4 with postmortem confirmation. The material thus derived from 58 cases is discussed. The loss of vision may be sudden or gradual. Both half-fields may be affected at the same time or in succession. The common mode of onset is a sudden loss of both half-fields. The most frequent prodromal symptoms are attacks of vertigo and transient episodes of visual impairment. Permanent blindness occurs in a quarter of the cases.

The pattern of the visual fields when there is partial sparing or recovery of vision indicates that the area most often preserved corresponds with, or lies within, a circle extending to about 10 degrees from the fixation points. In the more peripheral parts of the visual fields, the sectors adjacent to the vertical meridian are not infrequently spared when there is loss of the remainder. Selective loss of central vision is rare. Psychological disorder, including spatial disorientation, visual agnosia, denial of blindness, visual hallucinations, and other symptoms, is an inconstant, but sometimes conspicuous, feature of the syndrome. The anatomic basis of the visual field defects is discussed, and the arterial blood supply to the visual cortex and optic radiations is considered in relation to the clinical and pathological data. The pathogenesis of the syndrome is discussed with special reference to the occurrence of simultaneous loss of vision in both halves of the visual fields and the postmortem finding, in some patients, of thrombosis in the basilar or vertebral arteries. The conclusion is drawn that the most frequent cause of bilateral occipital lobe infarction is embolism of the calcarine arteries. The emboli may result from valvular disease of the heart, auricular fibrillation, or coronary thrombosis but are more often derived from thrombi formed within the basilar or vertebral arteries as the result of atherosclerosis.

THERAPEUTICS

Phenolic Compounds in Chemotherapy of Rheumatic Fever. N. E. Clarke, C. N. Clarke and R. E. Mosher. Am. J. M. Sc. **235**:7-22 (Jan.) 1958 [Philadelphia].

Compounds related to the monophenol salicylic acid, i. e., the diphenols gentisic acid, protocatechuic acid, 2,3-dihydroxy benzoic (pyrocatechuic) acid, beta resorcylic acid, and gamma resorcylic acid, and the triphenols phloroglucinol carboxylic acid and 2,3,6-trihydroxy benzoic acid, were tested in patients with rheumatic fever and rheumatoid arthritis. Increased antirheumatic potency was observed in phenolic compounds with double chelate rings, and superior antirheumatic qualities were associated with a second or third hydroxyl group in the 3 position on the benzene ring. The compounds that had double chelate rings or a single chelate ring and hydroxyl group in the 3 position did not generate usual urinary changes associated with detoxication. The phenolic compounds produced some changes associated with antirheumatic adrenal hormones but differed by producing relative increases in circulating lymphocyte cells and decreasing the urinary excretion of 17-ketosteroids.

The high antirheumatic potency of double chelating phenols supports the importance of antirheumatic metabolites in salicylic acid therapy. The compound 2,3,6-trihydroxy benzoic acid had lower toxicity and acted more promptly to suppress manifestations of rheumatic fever and lower elevated blood sedimentation rates than did all other phenolic compounds. Like other double chelating phenols in this series, it usually decreased urinary excretion of sulfur and glucuronic acid conjugates except in patients who had malignant or submalignant rheumatic fever. These metabolic findings suggest a normalizing or saving action on special connective tissue components. The compound 2,3,6-trihydroxy benzoic acid also produced significant and consistent reduction in the urinary excretion of 17-ketosteroids, which lends support to its having a saving action in rheumatic fever. These observations permit the belief that triphenols and especially 2,3,6-trihydroxy benzoic acid, when administered early in a first attack of rheumatic fever, bring unusually rapid recovery without residual signs of heart damage.

BOOK REVIEWS

The Pharmacologic Principles of Medical Practice: A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine. By John C. Krantz, Jr., Professor of Pharmacology, School of Medicine, University of Maryland, Baltimore, and C. Jelleff Carr, Senior Research Pharmacologist, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md. Fourth edition. Cloth. $14. Pp. 1313, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

This new edition has been enlarged by 150 pages. Although much has been rewritten, the organization remains the same. The first portion of the book discusses, in some detail, the historical background and general principles of drug action. The numerous examples used for the latter may be considered repetitious and unnecessarily elementary by some physicians and medical students, although for students in pharmacology and other fields this portion may be very helpful. The remainder of the volume is divided into eight major therapeutic categories. A new chapter on the local use of drugs in the ear, eye, nose, and throat includes a variety of agents useful in these specialized fields. The chapter on the use of drugs in the treatment of mental illness reflects the recent advances in this area. Antihistaminic drugs are no longer considered with autonomic agents but are included in a new chapter on allergic diseases. The outstanding feature of the book appears to be its comprehensive inclusion of almost all of the drug preparations used in medicine today. They are identified by both generic and proprietary names, and for all official and many nonofficial agents the available preparations are described. The index has been enlarged and is more useful than in previous editions. Despite frequent reference in the text to original papers by author and year, bibliographic references at the end of each chapter are limited and refer only to general or review articles. The organization of the material results in many drugs being mentioned in several spots throughout the book without any adequate discussion of the agent. This book would probably be of most value to persons in fields related to medicine, where a comprehensive but rather superficial consideration of pharmacology would be helpful.

Medicolegal Forms with Legal Analysis. Paper. pp. 111. Law Department, American Medical Association, 535 N. Dearborn St., Chicago 10, 1957.

A review of professional liability claims shows that a significant number might never have been initiated if the physician had obtained an adequate written consent. This fact, plus the lack of up-to-date medicolegal forms, apparently motivated the Law Department of the American Medical Association to prepare this booklet. The material is discussed under the following headings: (1) Consent to Operations and Other Procedures; (2) Patient's Right to Privacy; (3) Confidential Communications and Records; (4) Artificial Insemination; (5) The Physician-Patient Relationship; and (6) Autopsy. Each section includes case citations and numerous authorization and consent forms which physicians or their attorneys may modify to suit their needs or to meet the requirements of local laws. Although the Law Department states that the booklet is not exhaustive, it is probably the most comprehensive publication on medicolegal forms available. Every practicing physician and attorney in the medicolegal field would be well advised to obtain a copy. He may do this by writing to the Law Department. Single copies are available to members of the American Medical Association without charge. Others may obtain copies for $1.00 each.

Measurement in Physical Education. By Donald K. Mathews, D.P.Ed., Associate Professor and Director of Research in Physical Education, State College of Washington, Pullman. Cloth. $5.25. Pp. 359, with 81 illustrations by Todd Wallis. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1958.

The growing interest in fitness and its evaluation makes this a timely volume. The author has geared the book to the level of prospective teachers of physical education. At the same time, he has included sufficient statistical method to permit students to become capable of scientific testing and application of results. After a discussion of approaches and methods of measurement, there is good coverage of strength tests, motor fitness and motor ability tests, sports skill tests, and body mechanics evaluation. Cardiovascular testing and nutritional appraisal are considered in terms of the physical educator's responsibilities in these areas. Evaluation of social efficiency and testing of knowledge in health and physical education are less extensively treated. There is a summary relating to the organization and administration of the testing program.

This volume should gain wide acceptance for use at the undergraduate level. Its understandable language and nontechnical approach will be appreciated by students. Moreover, its coverage is adequate in terms of the future responsibilities of the average student in the testing area. Appropriate emphasis is given to application of the tests to the

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instructional program in physical education. It would have been advisable, however, to confine coverage to physical education and directly related testing. Evaluation in health education deserves a broader and more comprehensive treatment than is here offered. If physical educators are to have responsibilities in the school health program, they should be thoroughly prepared for these duties. The author's recognition of the limitations of available testing devices is refreshing. He makes a good point in asserting that, while it would be foolhardy not to admit the shortcomings of present procedures, it would be even more foolish not to test merely because today's tests are not perfect. Testing is a means toward a better physical education program, not a program or an end in itself.

Biochemistry. By Abraham Cantarow, M.D., Professor of Biochemistry, Jefferson Medical College, Philadelphia, and Bernard Schepartz, Ph.D., Assistant Professor of Biochemistry, Jefferson Medical College. Second edition. Cloth. $12. Pp. 867, with 150 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1957.

This volume is written for first year medical students. The authors felt that there was a need for a biochemistry textbook that would stimulate interest in this difficult field. The medical student frequently feels the lack of adequate preparation in the fundamentals of organic and physical chemistry, and the authors, in an endeavor to hold his interest, have used theory only when necessary and have stressed biochemical processes as they relate to metabolism or to normal and disturbed function. Biochemistry is a rapidly changing field, and difficulties are frequently encountered in integrating the many areas of specialized research into the whole of biochemistry without stressing or overemphasizing any one of them. The authors have tried to give fairly complete presentation of each subject without being sidetracked by details. They make use of cross references to the details of topics that frequently reappear throughout the text.

The first five chapters give a relatively brief description of the chemistry of carbohydrates, lipids, proteins, nucleic acids, and porphyrin compounds. This is followed by discussions of the vitamins and enzymes; the mechanisms of digestion, detoxification, respiration, water balance, and acid-base balance; methods used for metabolic investigation, energy metabolism, high-energy phosphate bonds, biological oxidation; and carbohydrate, lipid, protein, nucleic acid, porphyrin, and inorganic metabolism. The last chapters deal with hormones, tissue composition, milk, blood and other body fluids, and various aspects of renal function. Each chapter contains a bibliography, which consists of a list of monographs or books of general interest rather than papers on isolated experimental work of limited interest. The table of contents and the index are complete.

Chemical Methods in Clinical Medicine: Their Application and Interpretation with Techniques of Simple Tests. By G. A. Harrison, B.A., M.D., B.Ch. Fourth edition. Cloth. $11. Pp. 667, with 164 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W. C. 1, England, 1957.

This textbook is primarily a record of the author's personal experiments and opinions, and, for this reason, references to the literature have been restricted to special points or particular techniques. The first chapter deals with special apparatus, such as the colorimeter, the flame photometer, paper electrophoresis, and the spectroscope. Succeeding chapters deal with routine urine examinations, as well as normal and abnormal urinary constituents and renal function tests. Blood sugar levels, glucose tolerance curves, liver and pancreatic function tests, blood, spinal fluid, milk, and gastric analyses, and the chemical examinations of duodenal contents and feces are described. A discussion on basal metabolism and a chapter on the laboratory diagnosis of abnormal skin pigmentation is presented. The last chapter deals briefly with special tests and problems, including tests for seminal stains, blood stains, and tests for amyloid, splenic anemia, and lipoid histiocytosis. The methods for preparation of reagents and their standardization, conversion factors, logarithm and antilogarithm tables and other miscellaneous matters are collected in the appendix. The book is written in an easily readable, relatively informal manner. The illustrations are well chosen. This book is a collection of observations and favorite methods of the author and is not intended to be a complete manual. For this reason, it should be of greatest value as a reference guide for the clinician rather than for those engaged in the various special phases of laboratory medicine. Within these limitations, the author's intent has been well fulfilled.

Advances in Tuberculosis Research [Volume VIII:] BCG: A Discussion of Its Use and Application. Edited by Dr. Hans Birkhäuser and Dr. Hubert Bloch. Cloth. $11. Pp. 316, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; S. Karger AG., Arnold Böcklinstrasse 25, Basel, Switzerland, 1957.

This volume, the eighth in the series, emphasizes the controversial questions concerning BCG vaccine. It presents studies in progress and discusses problems of theoretical and practical importance. The editors express their hope that these contributions will be helpful in stimulating discussion and orienting further studies. It is now more than 25 years since BCG vaccine was first introduced. The vaccine has been given to probably well over 100 million persons all over the world. There is still no standard preparation of the vaccine nor has a vaccination technique been generally standardized. There is no agreement as to the usefulness and efficacy of BCG vaccinations. There are wide differences of opinion with regard to vaccination

methods, and preparation of the vaccine varies widely from one laboratory and one country to another. Even where the vaccination is compulsory by law, variations exist in kind of vaccine, method used, and indications and contraindications governing its administration. Scientific evaluation of the effects has just begun in most countries. Workers again are becoming interested in the mechanism of its action. Experimental findings are often controversial. National and international cooperative projects are being carried out.

The editors did not attempt to present a summary of results of completed studies but rather to present publications that would expose current problems, to describe new techniques differing from those accepted, and to include examples of performing the vaccination in the field under various and often adverse conditions. This valuable volume not only should help resolve the many questions concerning BCG vaccination for the student but also should stimulate the ultimate solution of the problems involved.

Artificial Insemination in the Human. By A. M. C. M. Schellen, M.D. With introduction by Sophia J. Kleegman, M.D., Associate Professor of Gynecology, College of Medicine, New York University, New York. Translation by Miss M. E. Hollander. Cloth. $14. Pp. 420, with 10 illustrations. Elsevier Press, Inc., Bank of Southwest Building, Houston 2; 110-112 Spuistraat, Amsterdam C, Netherlands; Cleaver-Hume Press, Ltd., 31 Wright's Lane, Kensington, London, W. 8, England, 1957.

This book was written by a European physician who accumulated much of his information while on a lengthy visit to the United States. The author has assembled a tremendous amount of data pertaining to artificial insemination and other phases of the management of infertility. The literature apparently has been thoroughly combed for references, and virtually every phase of the subject has been covered, including history, legal ramifications, methods, choice of donor, methods of analysis of results, and moral, sociological, and religious aspects of the subject. As a reference to published reports, the book is excellent. The excerpts are generally pertinent and well abstracted. On the other hand, in some instances, possibly through lack of complete familiarity with the language, the author has mistaken the content or purpose of some of the material he has abstracted. The book is essentially an analysis of the work of others. For this reason, it would seem somewhat injudicious for the author to reach conclusions, as he has attempted to do. It would have been better to leave the value or lack of value of the procedures to the judgment of the reader. Some of the statements regarding medical fees in America appear to be inaccurate. In general, however, the author has treated a controversial subject with tact and good taste and has performed a worthy service. It is only when he editorializes that one may take issue with some of his conclusions. The book should be read by anyone interested in artificial insemination.

Understanding Your Patient. Edited by Samuel Liebman, M.D., Clinical Assistant Professor of Psychiatry, University of Illinois College of Medicine, Chicago. Contributors: C. Knight Aldrich, M.D., and others. Cloth. $5. Pp. 170. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5; 4885 Western Ave., Montreal 6, Canada; Pitman Medical Publishing Company, Ltd., 45 New Oxford St., London, W. C. 1, England, 1957.

This is a series of lectures given before the staff of the North Shore Hospital in Winnetka, Ill., where the author is the medical director. One of three such monographs, it is written in understandable terms by physicians who specialize in the subjects presented. An attempt is made to present the material from a practical viewpoint, and, therefore, this should enable the physician to meet and understand the psychiatric and psychosomatic problems of his patients from day to day and to treat them intelligently. He may not be able on his own to solve all of these situations, but this book should at least enable him to recognize such problems and know when and where to call for help. The leading article, written by Dr. Blain, sets the stage well and implies that each practicing physician has a responsibility in this field. The series begins with the child and carries on to adult life, even to the point of advising how to handle grandparents. The articles on premarital and marital counseling are excellent. This book should make the thoughtful physician more aware of psychosomatic problems in his patients.

The UFAW Handbook on the Care and Management of Laboratory Animals. Edited by Alastair N. Worden and W. Lane-Petter. Second edition. Cloth. $9.80. Pp. 951. Published by Universities Federation for Animal Welfare, London, England; distributed by Animal Care Panel, Office of Editor, 951 E. 58th St., Chicago 37, 1957.

This second edition is a distinct contribution to the rapidly expanding area of our knowledge concerning laboratory animals. With 88 contributors and with a discussion of the care and handling of more than 50 animals that are used in the laboratory, the book is a mine of information. The numerous illustrations contribute to its value. The first 16 chapters discuss the general considerations pertinent to the efficient management of laboratory animals, including housing, breeding, record keeping, and the use of anesthesia. Chapters 17 through 75 contain detailed information about each of more than 50 species of laboratory animals. Some of the sections on disease are modest, and some of the chapters could have been proofread more carefully. The references in each chapter are themselves items of great value, and the work as a whole is probably the outstanding volume in print on the care of laboratory animals.

QUESTIONS AND ANSWERS

TESTING THYROID FUNCTION

TO THE EDITOR:—*Of the three determinations for thyroid function, namely, basal metabolism, protein-bound iodine, and radioiodine uptake, which is, at the present time, considered to be the most accurate? How do these tests compare with each other?*

W. J. Hinzelman, M.D., Greeley, Colo.

ANSWER.—The accuracy of any test of thyroid function is dependent largely on the attention to detail and the enthusiasm of the laboratory personnel in its performance. Failure to observe perfect technique in all details is undoubtedly one reason why the basal metabolism test has produced so many unsatisfactory results. It has been estimated that the basal metabolic rate indicates thyroid function correctly in only about 50% of cases, but with extra care this figure could be improved to 75 or 80%.

At the present time, the determination of protein-bound iodine is the most accurate method of assessing thyroid function. The test is difficult to perform and is subject to contamination from iodine in the air, water, and glassware. Its chief weaknesses are (1) the overlap of values in different states of thyroid function, and (2) the deceptive results produced by previous ingestion of iodine, thyroid, antithyroid drugs, mercurial diuretics, and triiodothyronine, by other disease states, such as acute hepatitis, acute thyroiditis, and nephrosis, and by pregnancy. The normal range for this test is 3-8 mcg. per 100 cc.

The determination of the 24-hour thyroidal uptake of I^{131} is the most commonly used test employing radioiodine. This method is subject to the same weaknesses as the determination of protein-bound iodine. In addition, because of the wide scatter in 24-hour I^{131} uptake, the test is unreliable in the diagnosis of hyperthyroidism caused by adenomatous goiter. Accuracy of the test may be improved by determining the 24-hour I^{131} uptake before and after the administration of triiodothyronine and thyrotropin. The normal range for the 24-hour uptake of radioiodine is 10-40%. Uptakes of over 55% usually indicate hyperthyroidism, and uptakes of between 40 and 55% represent the twilight zone—either euthyroidism or hyperthyroidism. This test has about the same degree of accuracy as the carefully performed basal metabolism determination.

The best comparison of the accuracy of the three tests in the diagnosis of thyroid dysfunction is that of Blackburn and Power (Tr. Am. Goiter A., p. 249, 1955). Their experience indicates that the protein-bound iodine test is more accurate than that of either the basal metabolic rate or the I^{131} uptake in the diagnosis of toxic diffuse goiter, adenomatous goiter with hyperthyroidism, and myxedema. The basal metabolic rate was more accurate than the 24-hour radioiodine uptake.

The diagnosis of thyroid dysfunction is made primarily on the clinical appraisal of the patient's history and physical findings. Laboratory tests by no means supplant clinical judgment but merely tend to support it.

FOURTH INOCULATION OF POLIOMYELITIS VACCINE

TO THE EDITOR:—*What has been the official recommendation regarding booster doses of poliomyelitis vaccine after an individual has completed the initial course of three injections? Is it now recommended that these be given after the third injection? If so, at what interval should they be given?*

W. C. Nowlin, M.D., Littlefield, Texas.

ANSWER.—At the time of writing, no "official" recommendations have been formulated by any national medical group concerning a fourth inoculation of poliomyelitis vaccine, but several investigators and some state health departments have recommended that such a dose be given as a routine. This problem requires careful consideration both from the public health standpoint and from the standpoint of the patient. Salk has reported the persistence of neutralizing antibodies for periods up to four and one-half years in persons immunized with three inoculations of research-laboratory-produced vaccine. Data presently available are inadequate to determine precisely the duration of artificial immunity induced by commercial vaccine. Although commercial poliomyelitis vaccines do not all reach the level of antigenic potency of research-laboratory-produced vaccine, the basic series of three inoculations with commercial vaccine has been shown to produce satisfactory antibody response. All available evidence points to a continuing vaccine effectiveness against paralytic poliomyelitis of about 75% among all vaccinated

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persons and of about 90% among those who have received three doses. Since there are still many persons who have not yet been vaccinated or who have received only one or two inoculations, the primary goal of public health programs must be the immunization of all persons under 40 years of age with the basic series of three inoculations. For this reason, many health departments have made no recommendation concerning a fourth dose but rather have emphasized the basic task of achieving primary immunization of all susceptible age groups with three doses.

From the standpoint of the patient, however, it may be entirely appropriate for the practicing physician to recommend a fourth dose. Many investigators are concerned that the series of three inoculations is not 100% effective. A few persons do not produce measurable antibody levels against one of the poliovirus types despite three inoculations of commercial vaccine. Furthermore, a small number of confirmed paralytic poliomyelitis cases have been documented in persons vaccinated three times. For these reasons, and since reactions to the vaccine have been remarkably few, the practicing physician may wish to recommend that his patients receive a fourth inoculation. It would be reasonable for a fourth dose to be given one or two years after the third dose or prior to periods of increased risk, such as before the next poliomyelitis season, prior to travel abroad, or when cases of poliomyelitis are occurring in the community.

EDITOR'S NOTE.—After the above reply was received and prepared for publication, a committee of advisors on poliomyelitis vaccination to the Surgeon General of the United States Public Health Service met in Washington, D. C. They emphasized the importance of the basic three-dose series for poliomyelitis immunization but agreed that the decision to administer the fourth poliomyelitis immunization inoculation must be made by individual physicians.

MODIFICATION OF MASTER'S TWO-STEP EXERCISE TEST

TO THE EDITOR:—*Concerning Master's two-step and "double-step" tests, is there any reason why exercise, such as toe touching on the electrocardiogram table until tired at a rate of perhaps one every 4 seconds, should not give just as satisfactory results?*

L. B. Lowe, M.D., Roanoke, Va.

ANSWER.—Dr. Master, the originator of the "two-step" exercise test, feels that this procedure should be standardized. His first argument is that if too little exercise is performed, even in the presence of coronary disease, there may be no changes on the electrocardiogram and that if too much effort is essayed it might be dangerous to the patient. Moreover, again and again it has been demonstrated that the single (1½-minute) two-step test may result in negative findings while a double (3-minute) two-step test results in positive findings. This is another reason for standardization of the test. The need for standardization is further proved by having a patient who should perform, for example, 36 trips for his age, sex, and weight climb only 30 times. The tracings are negative, but, if repeated for 36 ascents (the number obtained from the standard table), the electrocardiogram becomes positive. This will hold true on repetition of 30 trips and then 36. If unstandardized tests are to be essayed, a study first should be done on a control group of normal persons before the test is applied to patients suspected of suffering from coronary disease or some other condition involving the coronary circulation.

TUBERCULIN TESTING

TO THE EDITOR:—*What is the significance of a 4+ reaction and central necrosis with a Mantoux 1:10,000 interdermal tuberculin test in a middle-aged man with (1) an apparently normal chest, and (2) arrested or fibrotic minimal chest lesion? 3. Does a strongly positive Mantoux reaction point to extrathoracic tuberculosis if chest findings are negative? 4. Since streptomycin and isoniazid are often given for treatment of other than tuberculosis, does the tubercle bacilli become less virulent or not recoverable and also more resistant to those main drugs? 5. Does active antituberculosis treatment produce reversal or diminution of the interdermal test reaction?*

M.D., New York.

ANSWER.—The 4+ reaction indicates a high degree of sensitivity of tissue to tuberculoprotein, caused by tuberculous lesions containing living tubercle bacilli. They may be located both in the chest and in extrathoracic organs, depending on where the tubercle bacilli were focalized when they initially invaded the body.

1. It is assumed that the expression "apparently normal chest" refers to clear x-ray film and no abnormal physical sign. There may be many lesions in the lungs of this person which are not revealed by x-ray film or conventional physical examination. Lesions must be macroscopic before they obstruct x-rays so as to cast visible shadows on film. Moreover, they must have proper consistency to obstruct x-rays. Without this consistency, sizable lesions may be radiotransparent and therefore cast no shadow. Furthermore, such lesions must be in the 75% of the lungs visualized on the usual posteroanterior x-ray film of the chest. If they are located in the 25% of the lung hidden from view by the shadows of the heart and diaphragm, their presence is not revealed by shadow on the film. All chronic pulmonary tuberculous lesions are microscopic in the beginning, and, therefore, their presence and loca-

tions are not determined by x-ray film. In many persons such lesions never attain size and consistency or have the location to be detected by x-ray film. This is why the tuberculin test is far superior to the x-ray film of the chest in screening from any group of persons those who have tuberculosis in some stage of its development. It is only persons who react to tuberculin and, therefore, have at least microscopic lesions in whom clinical tuberculosis develops. Such development may occur within months after microscopic lesions are laid down from the first invasion with tubercle bacilli or at any subsequent time in life, including old age. Unfortunately, there is no way to determine whether this person with a 4+ reaction will or will not have such lesions evolve as months and years pass, except to examine him periodically. If this is the first time this person has been tested with tuberculin, there is no way to determine how long ago his tissues were invaded with tubercle bacilli. This could have been in infancy or at any subsequent time up to a few weeks before the test was administered. That all tuberculin reactors have at least small lesions was determined in cattle during the last decades of the 19th century. The findings of veterinarians and pathologists of that time have ever since been confirmed. Between 1917 and 1957 in the United States alone more than 4 million cattle were slaughtered and postmortem examinations made because they reacted to tuberculin. This has left no question in the minds of students of tuberculosis that lesions are practically always present in tuberculin reactors. Ghon did careful and complete postmortem examinations of the bodies of children who, during life, had no evidence of tuberculosis except the tuberculin reaction. However, he found lesions often scarcely the size of the head of a small pin in all but one (not completely examined) of the 184 bodies.

2. It is assumed that the phrase "arrested or fibrotic minimal chest lesion" has been proved to be tuberculous. There are numerous other etiologies of fibrotic shadow-casting pulmonary lesions, none of which can be determined by the shadow on the x-ray film. If the given lesion has been proved to be tuberculous, one would expect to elicit a tuberculin reaction. Probably the degree of reaction depends on the amount of tuberculoprotein being eliminated from lesions in the body. In all probability there are numerous lesions other than the one under consideration in this person's body which, even if not active and progressive, may be releasing tuberculoprotein in sufficient amount to maintain a high degree of sensitivity. In some persons with long-standing lesions, the amount of tuberculoprotein liberated diminishes and sensitivity of tissues decreases so that only slight reaction results from the tuberculin test. In fact, in some cases sensitivity reaches such low levels that it is not elicited by the usual test doses of tuberculin. Evidence is accruing which strongly suggests that in more persons than was formerly believed all tubercle bacilli disappear and sensitivity is completely lost.

3. The tuberculin reaction does not indicate location of lesions. It is probably rare that a tuberculin reactor does not have at least microscopic lesions both in lungs and in extrathoracic organs. The degree of reaction apparently is not determined by location of lesions.

4. When the major antituberculosis drugs come in contact with tubercle bacilli they have a suppressive effect, particularly on those that are multiplying. Therefore, the numbers of such organisms may decrease and be less likely to be recovered in sputum and other material. Tubercle bacilli in contact with drugs may become resistant to them. When two drugs are administered simultaneously, emergence of resistance may be postponed considerably.

5. The characteristic of tuberculous lesions, namely, loss of blood supply, obviously prevents drugs from reaching the organisms in necrotic material. Therefore, only organisms in vascular lesions are affected. If bacilli in such vascular lesions are suppressed and stop multiplying, less tuberculoprotein is produced and one might expect decrease in sensitivity of tissue. The best observations in this respect have been made on persons who have recently been invaded with tubercle bacilli and have been converted to tuberculin reactors. At the time the reaction can first be elicited, the lesions in various parts of the body are usually small and vascular. Antituberculosis drugs administered at that time may be expected to reach all organisms. In a few cases in which drugs have been administered to recent tuberculin converters, there has been reversion of sensitivity, at least to the usual test doses of tuberculin. As yet, there is no incontrovertible evidence that such loss of sensitivity indicates that all tubercule bacilli have been destroyed. There is the probability that they have been suppressed, however, to such low levels that they are not multiplying and liberating tuberculoprotein. Continued observations may reveal that when the drugs are discontinued sensitivity will return as bacilli regain their activity.

EFFECTS OF COOKING ON FOOD

To the Editor:—*In the field of nutrition, aside from psychological or sensory reactions including geographical and customary dietary habits, what arguments are there, if any, in favor of the cooking of food, aside from possibly the destruction of pathogenic organisms, provided that the natural food is properly reduced in size before mastication?*

C. D. Generales, New York.

Answer.—The destruction of pathogenic organisms seems to this consultant to be an extremely important reason for cooking food, particularly if

the source of the food leads one to be skeptical of its cleanliness. Cooking also increases the palatability of many foods and, in the tuberous vegetables, helps to break down the fibrous tissue. Heat increases the digestibility of certain nutrients. Heat will also destroy certain antimetabolites, such as avidin in raw egg white. It would seem to be undesirable to dismiss lightly the psychological and sensory reactions toward food, and, since cooking favorably influences these, there certainly is no contraindication to this method of food preparation. If one should happen to prefer raw foods and is sure of their cleanliness, there likewise would be objection to cooking them, but a middle course is usually best.

EXCESSIVE POTASSIUM INFUSION

To the Editor:—*In an 8-year-old child who shows dehydration and has normal kidneys, is there danger of potassium poisoning with the following therapy? Administration of 1,000 cc. intravenously of fluid containing 10% dextrose solution and the following electrolytes: 80 mEq. of sodium, 36 mEq. of potassium, 4.6 mEq. of calcium, 63 mEq. of chlorine, 60 mEq. of lactate, and 2.8 mEq. of magnesium, with a rate of flow of 500 cc. per hour.* *M.D., Kentucky.*

Answer.—The infusion of potassium into a child at a rate of 18 mEq. per hour involves a definite hazard of potassium poisoning. Grollman (Pharmacology and Therapeutics, ed. 3, Philadelphia, Lea & Febiger, 1958, p. 851) recommends that this salt be given at a rate not exceeding 20 mEq. per hour to an adult, with constant supervision for evidence of cardiac arrhythmia or hyperpotassemia. The rate indicated by the questioner would accordingly be excessive for an 8-year-old child.

ATROPHY OF SUBCUTANEOUS FAT AT SITE OF INSULIN INJECTION

To the Editor:—*Is there any way to avoid the depressed areas at the site of protamine zinc insulin injections due to the digestion of the adipose tissue layer from the insulin? In two patients, the thighs are markedly irregular in outline, which is quite disfiguring.*

M. F. Bossart, M.D., Akron, Ohio.

Answer.—Atrophy of subcutaneous fat at the site of insulin injections occurs frequently in children, not uncommonly in women, and occasionally in adult males. The disappearance of fat is apparently a local metabolic effect of insulin. No important structure is damaged, and the end result has no serious significance aside from the cosmetic aspect. Individuals who are susceptible to atrophy usually develop such with any type of insulin and in any part of the body in which insulin is used. Various suggestions have been made in an attempt to avoid atrophy due to insulin injection in susceptible persons. These include injection of insulin intramuscularly and the use of insulin which has been kept at room temperature rather than in a refrigerator. In regard to the former, patients may not like to use a longer needle and the deeper injection. In regard to the latter, there is considerable difference of opinion as to whether this measure is effective. In the light of present knowledge, the best course would appear to be as follows: 1. For sites of injection, use areas over the abdomen, flanks, and upper buttocks; thus, any atrophies which occur will not be exposed to public view. 2. Use insulin kept at room temperature, for what value that may have. 3. Inject the insulin well beneath the skin, using a ½-in. needle. 4. Shift the site of injection from one time to the next so that a given area 3-4 cm. in diameter does not receive insulin oftener than once in three or four weeks. Fortunately, if insulin injections are completely stopped in an area where atrophies have occurred, in a considerable number of patients slow restitution of subcutaneous fat takes place, although this may require two or three years.

TREATMENT OF OLIGOSPERMIA

To the Editor:—*Please comment and make recommendations on management and prognosis in the following case. A young couple in their late twenties have been married eight years and have not been able to bring about conception. The wife appears to be normal gynecologically in all respects (menses, pelvic examination, Rubin test, endometrial biopsies, and cervical smears). Her husband, however, has a decreased number of sperm. Three semen analyses, done at intervals of three to four months, revealed sperm counts of approximately 20 million per cubic centimeter, of which 75% were nonmotile. Prostatic massage revealed no abnormalities. This man has a negative history in regard to descent of the testes, chronic diseases, exposure to radium, or ingestion of chemicals. Also, laboratory tests revealed normal blood cell count, sedimentation rate, protein-bound iodine level, and basal metabolism rate. He has been taking 1 grain (60 mg.) of thyroid daily for the past three to six months with no noticeable benefit, and, similarly, no benefit was observed with large doses of vitamin B by mouth. No fern effect in his semen has been determined.* *M.D., New York.*

Answer.—The inquirer has performed practically all of the tests that any qualified specialist would recommend, and he should be commended for the conservative manner of treatment. If the patient has normal thyroid function, very little can be done to improve the spermatozoal motility and viability. Small doses of testosterone, 10 mg. daily by mouth, may be tried for a month. Two reports have ap-

peared claiming improvement after the administration of sodium liothyronine (Cytomel) in men with necrozoospermia who did not improve with thyroid treatment, but these results have not been substantiated by others. There is still a possibility that pregnancy will ultimately occur even though the husband's fertility is not improved. If a prognosis concerning the husband's status is desired without further delay, a testicular biopsy may yield a clue regarding the character of the lesion involving the seminiferous tubules and its reversibility.

ANSWER.—The therapy of oligospermia, especially when 75% of cells are nonmotile, cannot be attempted until good morphologic examination has been made. Should morphology studies show that the majority of spermatozoa are abnormal, it would be wise to consider such a male sterile for all practical purposes, but with normal morphology, and especially when the motile cells show a good grade of motility, therapy might be of some benefit—perhaps testosterone rebound therapy. In the wife, accurate timing of ovulation could be attempted with the hope that the few cells which may be normal will be present at the correct time. With oligospermia, homologous insemination is usually of no help. After an eight-year period of infertility, if there is no religious prohibition, donor insemination should be strongly considered.

ACNE AND UNCONTROLLABLE DESIRE FOR SWEETS

TO THE EDITOR:—*What does one do for a 15-year-old boy who has acne vulgaris of face and back and an insatiable and uncontrollable desire to eat sweets? The parents are intelligent, and the son has a good IQ, but no pleading or argument can keep the boy from eating candy before meals, after meals, and at any and all hours. The parents have sought aid from psychologists and internists without success. Is there any known substance which can control the appetite for sweets? Amphetamine combinations have been used in control of appetite for foods in general.*

Horace A. Hall, M.D., Corona del Mar, Calif.

ANSWER.—Insofar as control of the acne is concerned, the eating of candy is not an impossible situation. If the boy will avoid chocolate, his desire for sweets should not interfere with the cure of his cutaneous condition. Whether x-ray therapy, estrogen administration, or antibiotic therapy is the treatment of choice or what local therapy should be prescribed depends on many factors, such as the severity of the eruption, the tendency toward scarring, the amount of pustulation present, and how much the patient and his parents are concerned about this cosmetic defect. Perhaps of greater importance is the habit pattern being developed by the boy. It is too late now to correct a serious character defect by simple parental discipline. If he cannot develop self-control by himself, the aid of a psychiatrist should be sought. Suppose the boy should develop an overpowering desire for alcohol or any other of the so-called social vices?

RAPID PROSTATIC GROWTH

TO THE EDITOR:—*In practice, one occasionally encounters male patients, usually 50-60 years old, in whom the prostate seems to grow rapidly. One man in particular, aged 55, has had two prostatic resections. Such patients apparently have less hypertrophy of the nipples than is average for men of corresponding age. Please comment on the desirability of giving female hormones to prevent recurrence of benign hypertrophy of the prostate. Please supply references for correlation of breast changes in older males with hormone changes. What is the effect on sexual activity of temporary use of female hormones on males?*

Frank C. Green, M.D., Chillicothe, Ill.

ANSWER.—In this age group it is not too unusual to have continued hypertrophic growth of the prostate, particularly after inadequate prostatic resection. This growth may even recur after enucleation. The cause or causes of benign prostatic hyperplasia are obscure. Sommers gives a good discussion of this problem (*Am. J. Path.* 22:185, 1956). Since there is some evidence that decreased androgens with relatively increased estrogens and perhaps additional adrenocortical steroid hormones are responsible for prostatic hyperplasia, female hormones would hardly be expected to prevent recurrence of benign hypertrophy. Some urologists feel that estrogens given preoperatively reduce bleeding during prostatic surgery. Most breast changes clinically observed in older males are the result of estrogens given for carcinoma of the prostate. The use of these female hormones in males in amounts of 3 mg. daily usually diminishes sexual activity, which returns to pretreatment levels several weeks after withdrawing the hormone.

LACERATION OF THE SPLEEN

TO THE EDITOR:—*What positive signs are available by physical examination, x-ray studies, and other methods to aid in making a diagnosis of laceration of the spleen where extensive hemorrhage has not occurred and where an enlarged spleen due to intracapsular hemorrhage is not demonstrated?*

Leon A. Frankel, M.D., Philadelphia.

ANSWER.—This consultant knows of no physical or x-ray signs of laceration of the normal spleen "where extensive hemorrhage has not occurred and where an enlarged spleen due to intracapsular hemorrhage is not demonstrated." A high index of suspicion would be history of a traumatic injury to

the chest or upper abdomen on the left, plus a localized pain similar to those experienced when an infarction of the spleen occurs. The limitations of the question must be interpreted as so minor a degree of "laceration" that the splenic capsule has not been punctured and yet the trauma has been insufficient to produce an intracapsulary hemorrhage. Such lesions should be self-healing under the circumstances, and none of the more classic signs of laceration of the spleen would develop.

ARTHRITIC NECK PAIN

To the Editor:—*What is the best treatment for pain in the left side of the neck due to arthritis? X-ray pictures show calcification drawing the vertebrae closer together on that side. Nothing will relieve it except cortisone tablets and ACTH tablets, containing 3 or 4 mg., taken each day. Would cutting the nerve or ultrasonic therapy help?*

M.D., Illinois.

Answer.—It is impossible to give any advice regarding the pain in the left side of the neck without knowing the type of arthritis causing it. The most frequent forms of arthritis in this area are rheumatoid spondylitis and osteoarthritis. X-ray therapy is most useful for the former. The latter is frequently associated with vertebral disk disease. In general, the treatment of this consists of a neck support (a four-poster cervical support), moist heat, salicylate therapy, and x-ray therapy. If the disk disease gives intractable pain, operation may be necessary as a last resort.

CONTACT LENSES

To the Editor:—*Is there any danger in the wearing of contact lenses, especially the newer "non-contact" contact lenses for which claims are made that they do not touch the eye surface and yet are still apparently invisible?*

M.D., Illinois.

Answer.—There are two chief types of contact lenses: scleral and corneal. The scleral type overlies the sclera and cornea with a well-marked difference in curvature marking their junction. It is worn with a layer of fluid between the lens and the cornea. A modification of this type of lens is the lacrimal type, which is molded in a single curve extending over both the sclera and the cornea. It is fitted much closer to the eye than the ordinary scleral type, and the tears constitute the fluid between the cornea and the inner surface of the contact lens. The corneal lens is a thin wafer worn directly on the cornea and held in position by the capillarity of the tears; it does not require the addition of any fluid. Corneal lenses are used only in eyes in which the curvature of the cornea is relatively regular. Marked corneal astigmatism may require the use of a scleral lens.

The chief medical indication for contact lenses is a regular astigmatism caused by a corneal abnormality in which the maximal optical correction is not obtained with ordinary lenses. The commonest condition in this category is keratoconus, in which contact lenses often yield a surprising improvement in vision. Occasionally, a regular astigmatism due to corneal scarring is neutralized with contact lenses. Additionally, individuals who have had a cataract operation in one eye and retain relatively good vision in the other are frequently able to obtain binocular vision. Certain individuals with marked refractive errors, frequently myopia, may prefer contact lenses for their occupation or avocation. Professional entertainers and athletes are frequently better able to participate in their activities with contact lenses. Athletes in body-contact sports frequently use them, and there is no great danger involved since the contact lens is cushioned on the globe symmetrically and protected by the same structures which protect the eyes.

Many individuals cannot wear contact lenses because of narrowness of the palpebral fissure, tightness of the lids, nervousness, or conjunctival irritation. These lenses are probably contraindicated in patients with glaucoma, since the corneal edema of glaucoma is identical with that caused by contact lenses. Unless there is an optical reason which outweighs the seriousness of a recurrence of the original disease, they should not be worn when the cornea has been the site of inflammation, particularly that arising from the herpes simplex virus. They are definitely contraindicated in neurological conditions which have caused a corneal anesthesia. Individuals in whom the conjunctiva becomes infected or injected with slight provocation are poor candidates, as are those with a history of episcleritis. Unless there are definite optical indications, the lenses are not recommended for persons with presbyopia, since additional correction must be worn for close work. Many patients, after wearing them a short time, particularly when they are being used only to satisfy vanity, become discouraged and discontinue wearing them. Despite the large number prescribed in recent years, surprisingly few people wear them regularly.

There are two main difficulties that occur when contact lenses are worn: irritation of the cornea and conjunctiva and corneal edema. Irritation arises from the presence of a foreign material beneath the lid and commonly prevents some individuals from ever wearing them for a useful length of time. The irritation may begin as soon as the lens is inserted and is not relieved until it is removed. Local anesthesia does but little to relieve the symptoms. As the eye becomes more tolerant of the irritation, the contact lens can be worn for longer and longer periods before irritation, photophobia, or lacrimation requires their removal. Edema of the cornea is a subepithelial diffuse haziness which occurs a

variable time after wearing the lens. Its occurrence is extremely uncommon after wearing the corneal type of lens and occurs in nearly all patients who wear the scleral type of lens. Contact lens wearers should be warned against persistence of wearing the lenses once there are symptoms of irritation or corneal edema.

PROTHROMBIN TIME IN JAUNDICE

To the Editor:—*A jaundiced patient has a prothrombin time of 17 seconds. The normal control prothrombin time is 14 seconds. Is this 3-second difference sufficient to cause hemorrhage at operation? If not, at what prothrombin time will hemorrhage occur?* *M.D., New York.*

Answer.—If any prolongation of the prothrombin time is observed in a jaundiced patient, an attempt should be made to determine the cause of the hypoprothrombinemia. If it is due to vitamin K deficiency, which is often observed in obstructive jaundice, the administration of a water soluble vitamin K compound, such as menadione given orally, will promptly elevate the prothrombin level and bring the prothrombin time to normal. A patient with obstructive jaundice may have only a slightly prolonged prothrombin time yet bleed excessively postoperatively if not given vitamin prophylactically, because the prothrombin level may decrease drastically due to the poor store of vitamin K in the body. With a prothrombin time of 17 seconds, no bleeding is apt to occur at operation, but in the untreated patient the bleeding may begin after 24 hours or even later.

An elevated prothrombin time which is not corrected by vitamin K therapy in a patient with jaundice usually indicates impairment of liver function. In such a patient, vitamin K has probably little beneficial effect and large doses may actually be harmful. A patient with a prothrombin time of 17 seconds which is not corrected by vitamin K therapy is unlikely to bleed postoperatively.

PREGNANCY AND PREDNISOLONE

To the Editor:—*Please give information on the effects of prednisolone therapy on pregnancy. A patient has been taking this drug for a few years to control asthma. For some time, her daily dose has been 7.5 mg. Recently she became pregnant after doctors had assured her that it was safe. After three months she had a miscarriage. On examination it was found that the fetus had been dead for about three weeks. The doctors do not agree on the cause of the death. Could it be due to the steroid drug?*

M.D., New York.

Answer.—There is no evidence that prednisolone causes fetal death or early interruption of pregnancy. Therefore, this patient may safely take the drug during her next pregnancy if it is necessary. In this case, a careful search should be made to find a cause for the miscarriage, and if one is found it should, of course, be remedied if possible.

Answer.—It is extremely unlikely that the prednisolone had anything to do with the miscarriage. There is no reference in the literature indicating any adverse effect of this drug on pregnancy, although adrenal cortical steroids have been administered to pregnant women for various conditions, such as Addison's disease, the adrenogenital syndrome, and disturbances of the Rh factor. If the patient wishes to be certain that it will be safe to try to have another child, she should undergo a thorough examination that would take cognizance not only of her endocrine status but also of her general condition. There is a fourfold rise in blood corticosteroid level of normal women up to the time of delivery.

CLIMATE AND ASTHMA

To the Editor:—*Please furnish information on the possible effect of the climate on asthmatic bronchitis, the cough and wheeze that come on during frequent bouts of respiratory infections in a child. Asthmatic symptoms are not present in the absence of respiratory infections, and the child is free from colds during the hot summer months. Response to the usual antiasthmatic drugs is poor, and recovery is rapid and complete. Growth and development are excellent. It is said that such individuals benefit in the hot dry climate of the southwestern United States, Arizona in particular.*

Charles P. Barnett, M.D., San Francisco, Calif.

Answer.—Many children in whom respiratory infections appear to be the cause of subsequent or accompanying attacks of coughing and wheezing appear to benefit by moving to a warm, dry climate, such as exists in Arizona. Whether this is due to the climatic change per se, some emotional tension-producing conflict in the home that was eliminated by the move, or possibly something to which the child was allergic and left behind is not always clear. The psychosomatic factor is difficult to estimate. Also, many children have an underlying allergy which flares up with a concurrent infection. It is important, therefore, that the allergic status of the child be thoroughly determined before moving to another area where similar allergens may exist or, as in the case of pollen, be present in an even greater abundance because of the warmer climate is considered.

Assuming, in this case, that the cough and wheeze are entirely due to the mechanical effects of bronchial irritation and secretion as a result of infection, it is reasonable to expect that removal to a warm, dry climate where infection and reinfection are less than in a damp, cold climate with wide

variations in temperature and where overcrowding in overheated homes frequently exist should result in marked improvement. It must not be assumed, however, that respiratory infections are unknown in Arizona and other parts of the southwestern United States. They exist there, as elsewhere, although probably to a lesser degree.

Although a trial period is preferable, unfortunately it may take as long as a year to determine the benefit of such a change. It must be remembered that, if an underlying allergy exists, there is always the possibility that the child may become sensitized to his new pollen contacts.

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AIR EMBOLISM

To the Editor:—*Have there been reports of fatal air embolism due to delay in stopping the administration of intravenous fluids and permitting all of the fluid to run in and the needle to stay in place?*

M.D., Kentucky.

Answer.—There has been no recorded instance, to this consultant's knowledge, of fatal air embolism resulting from failure to remove the needle promptly after an intravenous infusion. Since the venous pressure in the vessels used for such infusions is usually positive, there is no tendency for air to be introduced.

TREATMENT OF PROTRUDING EARS

To the Editor:—*A patient has markedly protruding ears. She is able to conceal them with her hair but would, at times, like to change her hair style. Are there available adhesive substances which can be successfully used to hold the ears back? What are the names of such products, and where may they be obtained?*

Robert H. Schaeffer, M.D., Walla Walla, Wash.

Answer.—Protruding ears may be held against the head for short periods by the use of Dermatone cement, which is available in most large surgical supply houses. The use of this material is temporary in nature and might be found to be cumbersome and unsatisfactory. Since there is a successful operation for setting the ears closer to the head together with reconstruction of the anti-helix, which is usually missing in these cases, it is felt that the operation is far more desirable in that the ears are put permanently into normal position and permanently reshaped to normal configuration. This operation is performed by all qualified plastic surgeons.

NEUROVASCULAR SYNDROME

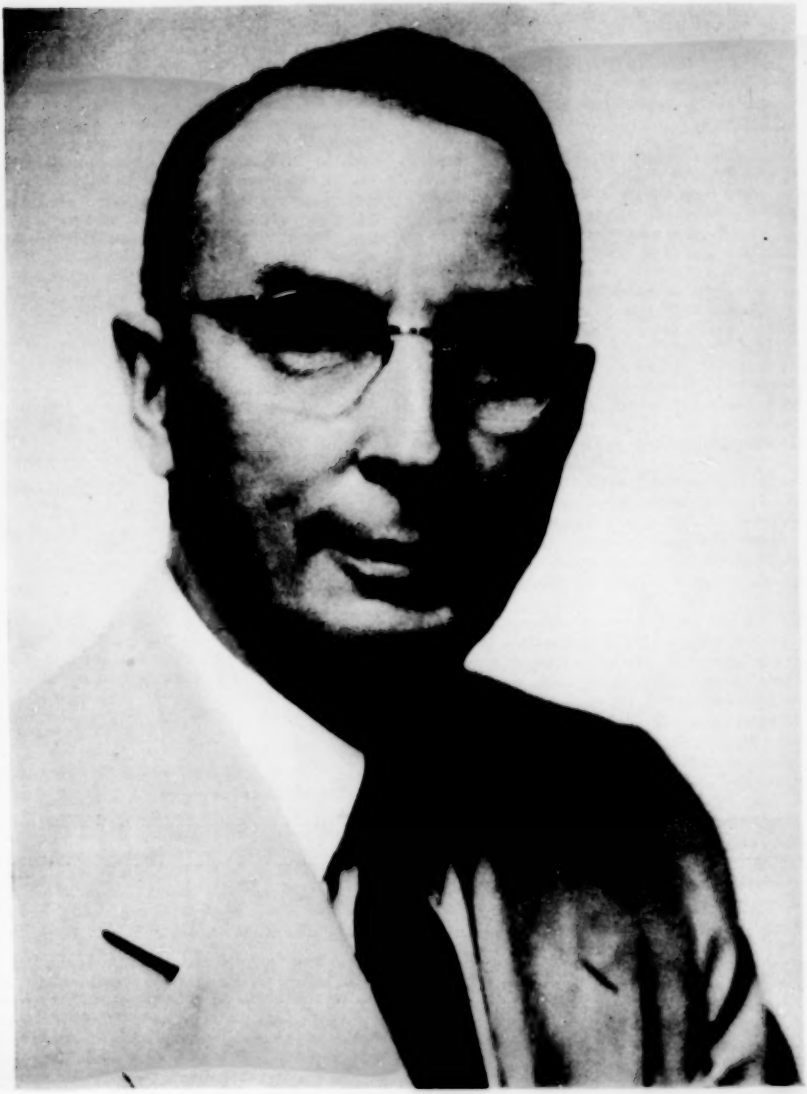
To the Editor:—*Why is the neurovascular syndrome not considered a single clinical entity?*

M.D., Illinois.

Answer.—The specific clinical entities encompassed by the inclusive phrase, neurovascular syndromes, are many. No entry has been listed in the Standard Nomenclature of Diseases and Operations for the syndrome because of its many etiological variations. Often some of these variations are delineated by special terminology, such as cervicodorsal outlet syndrome, cervical rib syndrome, scalenus anticus syndrome, costoclavicular syndrome, hyperabduction syndrome, subcoracoid pectoralis minor syndrome, first thoracic rib syndrome, or brachialgia statica paresthetica. All these symptom complexes have some signs and symptoms in common, but the basic factors responsible for the clinical manifestations vary and the types of treatment or correction of the condition are dependent on these causative agents.

While the phrase, neurovascular syndrome, is acceptable for medical communications, it should not be used for statement of diagnosis of a specific patient. If a specific diagnosis cannot be stated, the diagnosis listed and coded should be 080-Y00 Undiagnosed disease of upper extremity, generally, with supplementary term, 016 Causalgia, recorded as a manifestation. It is recognized that the determination of the specific disease entity may tax the diagnostic acumen and ability of the physician, but, unless this is done, treatment or correction of the condition becomes empirical. The condition must be differentiated from 221-912 Osteoarthritis of cervical spine, 978. .-4341 Compression of cervical nerve roots by protrusion of nucleus pulposus, or 2511-400.9 Herniation of intervertebral cartilage and even 000-X01 Anxiety reaction. The causative factor may be a Cervical rib 229-031 with 016 Causalgia, 241-017 Scoliosis of cervical or dorsal spine, congenital; 241-435 Scoliosis of cervical or dorsal spine due to thoracic disease; 241-5641 Scoliosis of cervical or dorsal spine following poliomyelitis or other cause; or 27.-430 Myositis due to posture (muscle to be specified). Other factors may be anomalies of trachial plexus, aberrant vascular supply, anomalies of scalenus anticus or medius muscles, kyphosis, faulty posture, compression of nerve or blood supply of arm by position of arm, new growths, aneurysms, and many others. It now becomes obvious that the treatment of the condition varies with the causative factor producing the symptom complex of pain, numbness, and discomfort in the shoulder and upper extremity and that to diagnose the condition broadly as "neurovascular syndrome" without the benefit of specific diagnosis is to do the patient an injustice.

V 1
195



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195

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